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AN INTERNATIONAL JOURNAL REPORTING THE PRACTICAL APPLICATION OF OUR NEWER KNOWLEDGE OF NUTRITION

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VITAMIN B_{12} *Excretion and* DIABETIC RETINOPATHY

By BERNARD BECKER, M.D., CALVIN A. LANG, A.B., AND BACON F. CHOW, PH.D.

THERE IS increasing evidence to indicate that vitamin B_{12} plays an important role, directly or indirectly, in carbohydrate metabolism.[1,2,3,4] These findings, together with the fact that the pancreas retains a high concentration[5] of radioactivity following the administration of vitamin B_{12}[6] labeled with radioactive cobalt (Co^{60}), prompted this study of the urinary excretion of vitamin B_{12} by patients with diabetes mellitus. Data demonstrating a possible relationship between administration of cortisone or testosterone and vitamin B_{12} excretion in man and rats are also included and their significance discussed.

STUDIES IN MAN

Design of Experiments

All patients used in this study except the control subjects suffered from diabetes mellitus of different degrees of severity. The diabetic patients were selected on the basis of a clear-cut clinical diagnosis of this disease with hyperglycemia and glycosuria. The first few subjects were chosen from a hospital in Mexico City; all others were drawn from the Diabetic Clinic and The Wilmer Institute of The Johns Hopkins Hospital. Only the Johns Hopkins group of patients were examined for retinopathy.* When the diagnosis of diabetes had been established and the presence or absence of retinopathy recorded, all patients were injected with a single dose of 50 μg. or 65 μg. vitamin B_{12} by the intramuscular route. Insulin therapy was not interrupted during the vitamin B_{12} studies. All estimations of vitamin B_{12} in urine were made microbiologically. Recovery of added vitamin B_{12} to a basal urine specimen was essentially quantitative, thus demonstrating the absence of inhibitor. Radioactive vitamin B_{12} was administered to several subjects. Radioactivity was measured in the urine either by superimposing aliquots of urine samples on the planchets directly or by extracting the radioactivity with butanol.[7] Previous experience[8] with healthy individuals indicated that collections of urine beyond the eight hours immediately after injection were not necessary, since the extension of the period by an additional 16 hours seldom yielded more than 5 per cent of the amount excreted in the first 8 hours. In the present study, 24-hour urines from a number of subjects were collected in order to be certain that this conclusion held in tests with diabetics. This was found to be so, and therefore only 8-hour

From the Department of Biochemistry, School of Hygiene and Public Health, The Johns Hopkins Univ. and The Wilmer Institute, The Johns Hopkins Hospital, Baltimore, Maryland.

The authors acknowledge with thanks the support of Merck and Co., Inc., the National Vitamin Foundation, Sharp and Dohme, Inc., and the Upjohn Company.

* All diabetic patients were examined with a giant ophthalmoscope following mydriasis. In this series those cases were included in which the fundi could be well visualized and in which no other ocular disease was present. Only the eyes with no evidence whatsoever of capillary aneurysms, exudates, or hemorrhages were classified as nonretinopathic.

TABLE I
Mexican Diabetics

Subjects	Male	Female	Average age	Vitamin B_{12} Excreted ($\bar{x} \pm SE$)*
			yrs.	μg.
Diabetics	3	2	37	4.9 ± 2.0
Controls	9	0	21	17 ± 1.7

* ($\bar{x} \pm SE$)—Mean and standard error.

specimens were utilized during the rest of the series. After the measurement of urine volume, aliquot samples were kept at 2–5° C. under toluene until ready for assay by the procedure of Skeggs and Wright.[9]

The samples were identified by code numbers at the hospital and analyzed. Only after completion of the assay was the ophthalmoscopic diagnosis of the patient compared with the analytical results. This procedure was adhered to rigidly in order to minimize bias.

Results

In the first study, five diabetic persons hospitalized in the Hospital de Enfermedades de la Nutrición in Mexico City* were given 65 μg.† of crystalline vitamin B_{12} intramuscularly. For comparison, 9 healthy Mexican subjects‡ were also injected with a like amount of this vitamin. The results of determination of the microbial activity in the urine excreted by these two groups are given in Table I. They demonstrate that the diabetics excreted much less vitamin B_{12} than the controls. These data with a limited number of subjects, not strictly comparable with respect to age and sex, prompted a more detailed study of vitamin B_{12} excretion in diabetics.

Work at The Wilmer Institute had indicated decreased adrenal cortical function in diabetics without retinopathy, and a possible causal relationship of relatively excessive adrenal activity to retinopathy and intercapillary glomerulosclerosis (the Kimmelstiel-Wilson renal lesion[10]). At the same time, some laboratory data from animal experiments became available, which indicated a possible interrelationship of the kidneys and adrenals with the metabolism of B_{12}. This combination of circumstances suggested the hypothesis that the urinary excretion of B_{12} by diabetics might be related to the presence or absence of retinopathy. To test this hypothesis, a total of 22 consecutive subjects with retinopathy and 13 without retinopathy were accumulated over a period of four months and each one given a vitamin B_{12} tolerance test. The distribution of the population with respect to age and sex is given in Table II.

TABLE II
U. S. Diabetics

Diabetics	Male	Female	Vitamin B_{12} excreted		
			25–45 yrs.	45–65 yrs.	65 yrs.
			μg.	μg.	μg.
Without retinopathy	2	11	3.3 (4)	5.5 (7)	1.3 (2)
With retinopathy	6	16	19 (6)	20 (9)	17 (7)

( )—Indicates number of subjects.

There was an uneven distribution with respect to the number of subjects in each group and a preponderance of females in both groups. In spite of this heterogeneity, the urinary excretion of vitamin B_{12} by all subjects fell into two distinct groups, as illustrated in Figure 1. In this figure, the urinary microbial activity of vitamin B_{12} in micrograms is plotted against age of the patient. It is clearly demonstrated that over the entire age range, there was a uniformly greater excretion by subjects with retinopathy than by those without. The two exceptions were subjects who were originally diagnosed as diabetics without retinopathy, but were found to have (or to have developed) early retinopathic changes on subsequent re-

* The authors wish to express their appreciation for the collaboration of Dr. Bernardo Sepulveda and his associates for this phase of our work.

† Squibb crystalline vitamin B_{12} solution with 0.5% phenol (65 μg. per cc.) was used.

‡ The authors wish to express their appreciation for the collaboration of Dr. Santiago Castro Estrada of E. R. Squibb and Sons, Mexico, in this phase of our work.

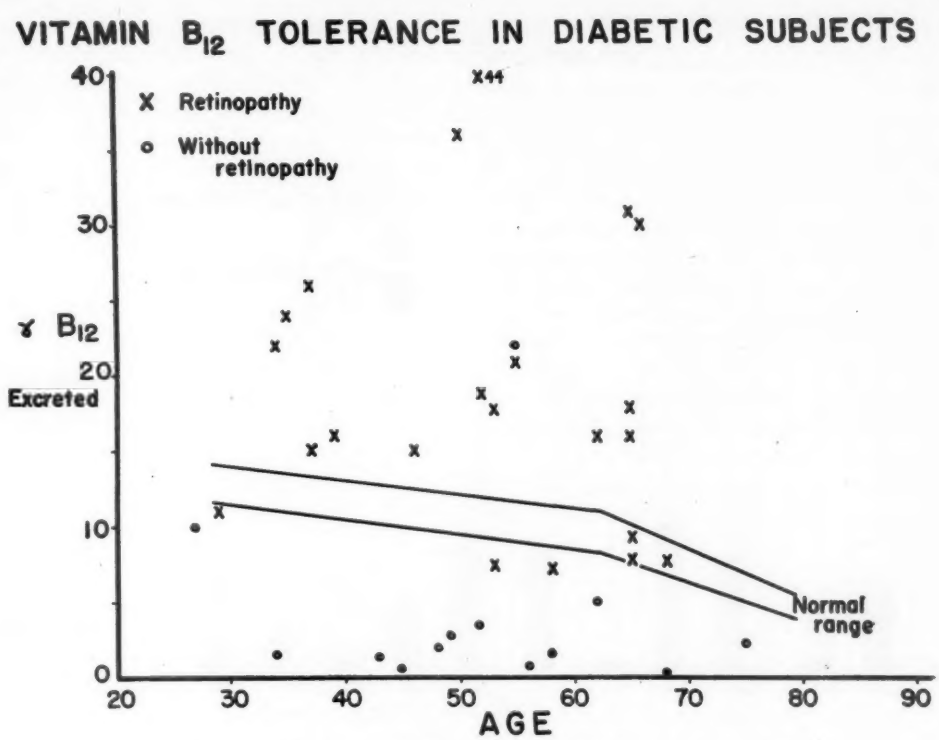

Fig. 1. The urinary excretion after intramuscular injection of vitamin B_{12}.

examination. However, in our statistical analyses (Table III) only the original diagnoses were considered. The urinary excretion of normal subjects was included for comparison. The data show that the diabetics with retinopathy excreted an average of approximately 19 μg. of vitamin B_{12}, and subjects without retinopathy excreted only 4.2 μg.; whereas the normal subjects excreted 9.6 μg. Statistical analyses indicate a significant difference, not only between the two groups with this disease, but also between either one of them and the healthy subjects.

Radioactive vitamin B_{12} studies revealed similar differences between the two groups of diabetics (Table IV). There was no correlation, however, between the severity of the retinopathy and the B_{12} excretion.

TABLE III

Urinary Excretion after Injection of Vitamin B_{12} (50 μg.)

Subjects	No. of subjects	Vitamin B_{12} excreted ($\bar{x} \pm SE$)*
		$\mu g.$
Diabetics without retinopathy	13	4.2 ± 1.7
Diabetics with retinopathy	22	19 ± 2.1
Healthy controls	6	9.6 ± 1.4

* ($\bar{x} \pm SE$)—Mean and standard error.

TABLE IV

Vitamin B_{12} Excretion and Diabetic Retinopathy

Group	No. of subjects	Vitamin B_{12} by radioactivity	Microbiological activity
		C. p. m.	$\mu g.$
With retinopathy	7	4150	17.5
Without retinopathy	4	1100	4.5

Endocrine Studies

Testosterone has been used in the management of diabetics with retinopathy.[11] It was, therefore, of interest to ascertain the effect of this hormone on the excretion of vitamin B_{12}.

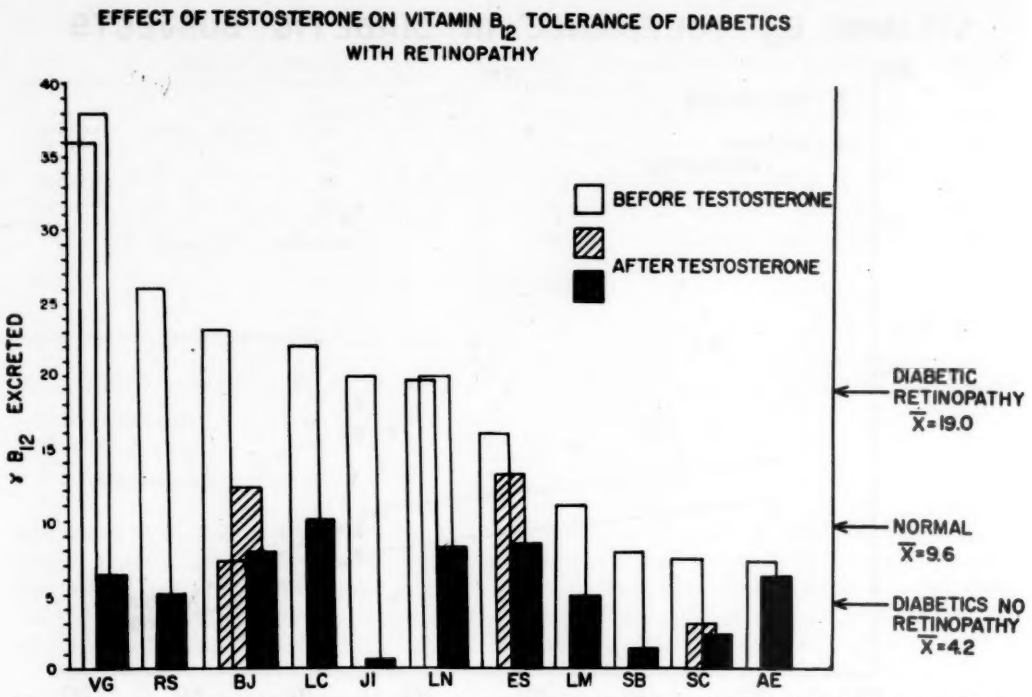

Fig. 2. The effect of testosterone on the urinary excretion following intramuscular injection of vitamin B_{12}.

To this end, a group of diabetics with retinopathy were first given one or occasionally two tests with vitamin B_{12} (50 μg.) to establish excretion levels before androgen therapy. After intramuscular injections of 100–200 mg. testosterone cyclopentylpropionate (Depo-Testosterone®)* every two to three weeks, these subjects were again given one or sometimes more tests for vitamin B_{12} excretion. Successive tests, when made, were at intervals of at least four weeks. Only after the completion of the microbiological assays for vitamin B_{12} activity in urine was the schedule of testosterone administration compared. The results of such a study are presented in Figure 2 as a bar graph. It was noted that among the 11 subjects studied there was in every instance a significant decrease in vitamin B_{12} excretion following the testosterone administration, although the magnitude of this decrease varied from one individual to another. Whether testosterone will likewise affect the excretion of vitamin B_{12} in nondiabetics, or in diabetics without retinopathy, remains to be established.

*The Depo-Testosterone® used in this study was generously supplied by The Upjohn Company, Kalamazoo, Michigan.

Animal Studies

Experimental Procedure

To further explore the interrelationships of vitamin B_{12} and adrenal cortical function it was of interest to ascertain, if possible, whether the excretion of vitamin B_{12} can be affected by administration of cortisone or of testosterone. To this end, a series of experiments was performed. In a typical experiment, three groups of female adult rats (4 each) raised in our colony, weighing about 220 Gm., were employed. The duration of the therapy in various experiments ranged from one week to one month. No marked differences in the results to be described below were observed at the different times of treatment. Group A received daily (except Sundays) 5 mg. of cortisone suspension per rat per day for three weeks. Group B received on the same days

an injection of 1 cc. of an isotonic saline solution instead of cortisone. These animals served as controls. Group C was given 0.2 cc. of a solution containing 50 mg./cc. of testosterone in peanut oil by subcutaneous injections every third day for two weeks. After this pretreatment, each animal in all three groups was given a test dose of one microgram of radioactive vitamin B_{12}.* Urinary specimens collected 24 hours before as well as 24 and 48 hours after injection were assayed for radioactivity and for microbiological activity of vitamin B_{12}. Forty-eight hours after the injection of vitamin B_{12} the animals were sacrificed and tissues such as liver, kidneys and 5.0 Gm. of muscle from the thigh were removed. Radioactivity in these samples was determined after wet ashing.†

Discussion

The low microbiological activity in the urine of diabetics without retinopathy might be explained on the basis of the presence of an inhibitor. This argument, however, loses its force since, in the studies in which radioactive vitamin B_{12} was administered, there was a similar marked difference in the urinary excretion of radioactivity by diabetics with and without retinopathy (Table IV). However, the complications arising from the unlabeled vitamin B_{12} reserve in the tissues of test subjects, as discussed in a previous report,[12] makes it unwise to interpret the data beyond a suggestion of a qualitative difference in the radioactivity in the urine specimens of these two groups of diabetics after administration of radiovitamin B_{12}. No efforts have been made to ascertain whether the microbiological activity excreted by the two types of diabetics is due to the presence of more than one form of this vitamin or of vitamin B_{12}-like compounds.

TABLE V

Radioactivity in Urine and Tissues

Groups	Treatment	Vitamin B_{12} in urine		Vitamin B_{12}* bound/gram tissue		
		R	M	Muscle	B Liver	Kidneys
				μg.	μg.	μg.
A	Cortisone	0.72	0.77 ± 0.03	0.11	5.7	167
B	Saline	0.44	0.48 ± 0.03	0.18	11.0	244
C	Testosterone	0.62	0.57 ± 0.04	0.11	7.7	118

R—Micrograms of vitamin B_{12} as measured by the radioactivity in the 24-hour urine specimen.
M—Micrograms of vitamin B_{12} as measured by the microbial activity in the 24-hour urine specimens.

Results

The results of a typical experiment, given in Table V, demonstrate that the vitamin B_{12} activity in the 24-hour urine specimens of cortisone-treated animals was almost twice that of the control animals, as measured either by the microbiological activity or by radioactivity. The testosterone-injected animals, however, showed no significant difference from the controls under these experimental conditions. The results of tissue analyses demonstrate that in every instance the organs of the cortisone-treated animals, and to some extent those receiving testosterone, retained less radioactivity than saline-injected controls.

Recently[13] a difference was reported in the excretion of vitamin B_{12} by young and old healthy subjects following injection of a test dose. This phenomenon may be attributed to the decrease of kidney or adrenal functions with age. A difference[12] in the rate of loss of radioactivity from the kidneys of young and old rats following subcutaneous injection of labeled vitamin B_{12} was also observed. These results suggest likewise a possible role of renal function in the excretion of vitamin B_{12}. Friedenwald and his associates[14] showed a correlation of Kimmelstiel-Wilson renal lesions with diabetic retinopathy. It is therefore plausible to attempt to explain the observation of the difference in vitamin B_{12} excretion by

* The radioactive vitamin used in all these experiments was kindly supplied by Merck and Company, Incorporated, on allocation from the Isotope Division of the United States Atomic Energy Commission.

† Marked hypertrophy of the uterus was observed at the time of necropsy.

these two groups of diabetics on the basis of the difference in the renal function. However, clinical tests of renal function did not correlate with vitamin B_{12} tolerance in this series of diabetic patients. The effects of testosterone on patients with diabetic retinopathy make this thesis even less likely. Nevertheless, the possibility of subclinical renal involvement affecting the vitamin B_{12} tolerance test requires further study.

Observations on the effect of cortisone on urinary excretion of rats suggest a possible explanation for the increased excretion of vitamin B_{12} in diabetic retinopathy. This hypothesis receives support from preliminary data demonstrating a high concentration of oxysteroids related to, but not identical with, cortisone in the urine of diabetics with retinopathy as compared to that of patients without retinopathy. In this communication it is merely intended to report the difference in the excretion of a test dose of B_{12} between these two groups of diabetics. The possible influence of the adrenal cortex, in so far as it is demonstrated by the increase in the excretion of vitamin B_{12} by rats treated with cortisone, deserves further investigation.

Such findings provide us with some of the necessary background information to study the biochemical and physiological defects in diabetics and may throw light on the metabolic function of vitamin B_{12}.

Summary

Following an intramuscular test dose of vitamin B_{12}, diabetic subjects with retinopathy excrete significantly more of the vitamin than non-diabetics; while diabetics without retinopathy excrete considerably less than the non-diabetics.

Administration of testosterone to diabetics with retinopathy decreases the urinary excretion of a test dose of vitamin B_{12}. Cortisone increases the test dose excretion of vitamin B_{12} in rats.

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Resumen

Excreción de vitamina B_{12} y retinopatía diabética

La vitamina radioactiva B_{12} no rotulada se administró por via parentérica a pacientes afectos de diabetes mellitus con y sin retinopatía. Se halló que los diabéticos con retinopatía excretaron alrededor del doble, y aquellos

sin retinopatía la mitad de la cantidad de la vitamina inyectada excretada por los sujetos sanos. La administración del testosterón a los diabéticos con retinopatía resultó en una disminución de la excreción urinaria de vitamina B_{12} al ser sometidos posteriormente a un test de tolerancia vitamínica.

En ratas normales, el tratamiento con cortisona por una a tres semanas resultó en un aumento de la excreción urinaria de la vitamina B_{12} inyectada. Estos datos sugieren una posible interrelación entre la excreción de vitamina B_{12} y las funciones de las glándulas suprarenales en los dos tipos de diabéticos. Esta opinión se halla aun más reforzada por el hecho de que las orinas de los diabéticos con retinopatía contienen una mayor concentración de oxisteroides relacionados pero no idénticos con la cortisona que las de los pacientes sin retinopatía.

The Child's Changing Appetite

"It is amazing that the average mother does not understand that her child has a normal desire for variation in the type of food he consumes. The mother will readily admit that at times she would prefer sandwiches and iced tea to a full meal, and she will admit that there are some days when she wants to eat dessert first and some meals when meat and potatoes simply do not taste good. However, she will refuse to agree that her child might have these same variations in preference for foods."

—P. Williamson. *GP* **8**: 57, 1953.

Philosophy of the First-Rate

"There is a philosophy which gives standards of value and judgment that apply to all spheres and activities of human life. It is a very simple one, and no one would reject it. I would call it the philosophy of the First-rate. Ask a doctor or a surgeon if he is ignorant of or indifferent to the best methods in his profession. Would he answer yes? Or would he consider that there are no differences of quality in art, literature, music, architecture, and that it does not matter whether a picture or a sonata or a play or a building is first-rate or third-rate? Or, taking the inquiry into a still more important province, do we think that when we apply the words good or bad to human character and conduct we are drawing meaningless and unimportant distinctions? In all fields of life all people, whatever their creed or race, admit what I called the philosophy of the first-rate. I have already quoted John Morley's saying that an educated man knew when a thing was proved and that an uneducated man did not know. I would prefer to say that an educated man knows, and an uneducated man does not know, what is first-rate, and that the best-educated man is he who knows the first-rate in the most important human activities."

—Sir Richard Livingstone. *British Medical Journal* **4834**: 454, 1953.

VITAMIN B_{12} SUPPLEMENTATION *of the Diet of* HEALTHY ADULTS

A STUDY OF WEIGHT CHANGES EMPLOYING A LATIN SQUARE DESIGN

By GILBERT M. BAYNE, M.D. AND WILLIAM P. BOGER, M.D.

VITAMIN B_{12} has been shown to produce a variety of effects in isolated tissues, bacteria, lower animals, and man. Among the more significant is the effect on growth and weight gain.

Vitamin B_{12} supplementation has a dramatic effect upon the weight gain of the progeny of rats maintained during gestation and lactation on a vitamin B_{12}-deficient diet.[1] If the deficient diet of the mothers is supplemented with 5 μg. of vitamin B_{12} per day, the enhanced weight gain in the treated young rats is only apparent in the last 30 days of a 90-day period of observation. This effect is thought to be related to vitamin B_{12} storage. Weight gain is probably due to appetite stimulation,[2,3] although this may not account for the entire effect.[2] It has been hypothesized that vitamin B_{12} plays a role in the transformation of carbohydrate to fat.[3] It has been shown also in mice[4] and rats[5] that the source of the calories may influence the amount of weight gain demonstrable during vitamin B_{12} supplementation. In summary of the animal data, it can be said that weight gain has been demonstrated as a consequence of vitamin B_{12} supplementation when there is (a) dietary deficiency including vitamin B_{12} deficiency, and (b) *ad libitum* feeding. The degree of response may be influenced by the source of calories in the diet.

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Attempts to demonstrate a growth-promoting effect in humans have met with varying degrees of success.[6-14] In general, the reports describing a positive effect upon weight gain or growth met the two requirements noted above for a positive effect in animals, whereas in many of the negative reports it is not certain that these criteria were met. It has been demonstrated in pregnant rats with the aid of vitamin B_{12} containing radioactive cobalt (Co^{60}) that both orally and parenterally administered vitamin B_{12} is transmitted to the placenta and to the fetus.[3] Whether this obtains in humans is not known.

PURPOSE

We were interested in studying the effects of vitamin B_{12} supplementation in middle-aged, healthy adults on an *ad libitum* diet where increased appetite and attendant weight gain might conceivably be a hazard to longevity rather than an index of good health, as it has been interpreted to be in early life.

In the past, when the function of a vitamin has been established, it has been incorporated with other known vitamins into multiple vitamin preparations. These are intended for prophylactic or therapeutic use during stressful situations where there is an increased vitamin requirement or a restriction in dietary intake. Multiple vitamin preparations are commonly used in association with low caloric diets in the therapy of obesity and are also

recommended in the management of pregnancy.

Although the foregoing information would not predict a response to vitamin B_{12} in individuals without evidence of or reason for deficiency, the magnitude of the clinical problem of obesity,[15] and the frequency of vitamin supplementation seemed to justify putting the problem to clinical test.

Method of Study

At the Norristown State Hospital the circumstances were such that a sufficiently large number of individuals could be followed for long periods of time on an *ad libitum* diet which was similar for all patients. The subjects participating in this study, who were in normal physical health, had been originally institutionalized because of mental illness. At the time of this investigation all patients were housed in one building reserved for those under observation prior to release from the institution. Previously published information on the weight changes associated with vitamin B_{12} administration indicated a need for reasonably large groups and the desirability of relatively long periods of study. These requirements seemed all the more important when dealing with groups in whom the likelihood of deficiency is slight. To further validate the observations for subsequent interpretation, the study groups were exposed to similar housing conditions and to the same diet. The vagaries of dietary intake were not felt to be any more varied in the patients selected for this study than would be anticipated for a similar-sized segment of the normal population. The influence on the study resulting from ability of the patient to select from the diet presented to him was minimized by the design of the study, which provided for the patient to be his own control.

Female patients from a single building who were fed in a common dining room were selected on the basis of the following criteria:

1. At least three months' residence in the building immediately prior to the initiation of the study and less than 5 lb. gain or loss within three months.

2. A likelihood of continued residence in the building for at least nine months.

3. No insulin shock or electroshock therapy during the period of study or during the three months prior to this.

4. No vitamin B_{12} supplementation during the three-month period prior to this study.

If at any time after the start of the investigation an individual failed to fulfill these criteria, she was dropped from the study. At the beginning, there were 75 subjects, three groups of 25, and at the conclusion of the study 44 persons, groups of 16, 14, and 14, respectively. Since the design of this work allowed each individual to serve as her own control, the patients who completed the study constitute a significant number. Weights were recorded for each patient at monthly intervals to the nearest $^1/_4$ lb. The patients were distributed within the three groups in such a manner as to assure comparable ages and initial weights. Fortunately, the necessity of eliminating individuals as the study progressed did not seriously modify the age or weight equality between groups (see Table II).

Each individual was allowed as much food as she desired at each regular mealtime. In order that variations among groups of patients and variations due to seasons of the year might be removed in the analysis of the data, a Latin square design[16] was used (Table I).

TABLE I

Groups	Patients	Periods			
		Jan. 15–Apr. 15	Apr. 15–July 15	July 15–Oct. 15	Oct. 15–Jan. 15
I	1–25	—	A	B	C
II	26–50	—	B	C	A
III	51–75	—	C	A	B

Treatment Schedules

Each patient received each schedule of treatment for three months.

A = Placebo (different in appearance from either of the other two).
B = 100 μg. of vitamin B_{12} once daily.*
C = Thirty cc. (30 μg.) of vitamin B_{12} elixir given three times a day before meals.*

*"Redisol"® Tablets and "Redisol"® Elixir were generously supplied by Sharp & Dohme, Inc., Philadelphia, Penna.

Vitamin B_{12} might influence appetite in a favorable direction either by relieving a deficiency state or by exerting a pharmacologic effect upon the utilization of ingested food. Accordingly, we compared a schedule of therapy in which vitamin B_{12} was administered once daily with a schedule calling for the administration of vitamin B_{12} before each meal.

Results

The results were recorded as the increase or decrease in weight from the end of one treatment period to another ($Y_{x+1} - Y_x$). The final weight gains or losses are shown to the nearest $^1/_4$ lb. in Table II.

The mean results for groups, periods and treatments are shown in Table III.

TABLE II

Group I

Patient	Age	Weight Y_0	Period (treatment) I (A) Y_1 minus Y_0	II (B) Y_2 minus Y_1	III (C) Y_3 minus Y_2
1	48	111	− 1.5	−4.25	2.5
2	40	145	− 5.5	5.5	0.0
3	50	136	0.75	3.25	4.5
4	36	99	− 9.5	3.0	1.0
5	53	147	− 3.0	3.5	−1.0
6	54	122.75	0.5	−1.0	4.75
7	55	122	− 2.5	−3.5	4.25
8	52	109	− 3.0	2.0	3.5
9	49	93	4.5	0.0	3.5
10	42	102	− 2.5	1.5	1.5
11	58	129	− 1.25	−3.75	4.5
12	60	126	− 2.25	2.75	3.5
13	45	105	− 2.75	2.25	1.25
14	33	114	−10.5	4.0	−5.0
Totals			−38.5	15.25	28.75
Means	48.2	118.6	− 2.75	1.09	2.05

Group II

Patient	Age	Weight Y_0	Period (treatment) I (B) Y_1 minus Y_0	II (C) Y_2 minus Y_1	III (A) Y_3 minus Y_2
1	48	130	− 6.75	−4.0	1.0
2	59	109.5	− 5.75	2.25	4.0
3	50	133	0.5	2.5	4.75
4	44	98	− 0.75	−1.25	−1.75
5	53	138	− 5.5	2.0	2.75
6	55	183	3.5	−3.5	10.0
7	51	124	− 3.0	−3.75	1.5
8	56	159.75	− 1.5	0.75	6.75
9	49	126	− 3.75	2.75	−2.0
10	42	123.75	0.5	1.25	1.25
11	58	112	1.0	3.5	3.25
12	62	98	− 2.0	0.0	3.5
13	53	174	6.75	4.0	4.0
14	44	134	4.0	−2.75	−3.25
15	46	158	− 2.25	−3.75	3.5
16	29	113	− 0.5	−1.5	2.5
Totals			−15.5	−1.5	41.75
Means	49.9	132.1	− 0.97	−0.09	2.61

Group III

Patient	Age	Weight Y_0	Period (treatment) I (C) Y_1 minus Y_0	II (A) Y_2 minus Y_1	III (B) Y_3 minus Y_2
1	40	103	−0.5	2.5	1.5
2	59	132.5	3.0	−0.25	−0.25
3	50	124.5	0.0	−1.75	−1.75
4	44	155.75	3.25	1.0	1.5
5	36	108.25	1.0	0.0	3.0
6	25	125	−4.75	1.75	−4.5
7	54	141.75	−3.75	−1.75	−1.5
8	41	147	5.5	10.5	2.0
9	51	112	−2.0	−2.0	4.0
10	47	187	2.75	−0.5	−0.5
11	42	136	−3.5	−3.25	−1.5
12	58	134	−0.5	1.0	3.0
13	63	159	0.5	2.5	4.25
14	32	93	−3.0	0.5	2.5
Totals			−2.0	10.25	11.75
Means	45.9	132.8	−0.14	0.73	0.84

TABLE III

Analysis of Weight Gain	*Lb.*
Treatment	Mean results
A	0.31
B	0.26
C	0.57
Period	Mean results
I	−1.27
II	0.55
III	1.87
Groups	Mean results
I	0.13
II	0.52
III	0.48

The mean weight gains were so nearly identical for the three treatments that no statistical analysis seemed necessary. The three groups of patients likewise showed comparable weight gains. The variation among periods probably reflects seasonal effects, the largest weight gains occurring in Period III, which included fall and early winter.

Discussion

These results illustrate the advantage of the particular experimental design employed. For example, the results for Group I show the following weight changes: (A) placebo, −2.75 lb.; (B) 100 μg. vitamin B_{12} once daily; +1.09 lb.; and (C) 30 μg. vitamin B_{12} three times a day, +2.05 lb. One would obtain a definite impression that vitamin B_{12} had a favorable effect. However, the results with Groups II and III would indicate that the apparent beneficial effect of vitamin B_{12} may be a reflection of an influence of seasons.

Likewise, the results for the three groups at the end of the first period are: (A) −2.75 lb.; (B) −0.97 lb.; and (C) −0.14 lb. Once again, there is a suggestion that vitamin B_{12} may be showing a favorable effect. However, the apparent favorable result does not persist in either of the last two periods. As a matter of fact, the placebo (A) showed the largest mean weight gain, +2.61 lb., in period III.

By using a Latin square design we were able to average out the effect of seasons and of groups of individuals, thereby obtaining a less biased comparison of the three treatments.

Conclusions cannot be drawn regarding the relative merits of the two schedules of vitamin B_{12} therapy employed, because neither schedule produced any weight gain in the individuals selected for study. Indeed, the question of appetite stimulation by vitamin B_{12} in adult human subjects, except as it has been dealt with in this study, remains unanswered. It remains for someone to employ larger oral

doses of vitamin B_{12} (1000 μg. or more) and to administer vitamin B_{12} parenterally before it can be stated that this factor does not stimulate appetite in the human adult.

Despite the negative results of the study here reported, this vitamin does exert profound metabolic effects that are beyond question.

(a) Vitamin B_{12} is necessary for the maintenance of a normal hematologic state by reason of its participation in nucleic acid synthesis. A part, if not the whole, of its activity in this regard is attributed to facilitation of the conversion of the pyrimidine base thymine to the nucleoside thymidine.[17] (b) The influence of vitamin B_{12} upon the integrity of the nervous system is attested to by the relief of combined system disease seen in pernicious anemia, whereas folic acid, which corrects the hematologic aspects of pernicious anemia, exerts no beneficial effects upon neurologic manifestations of this disease.[18] (c) A lipotropic effect has been clearly demonstrated in animals and may be related to the participation of vitamin B_{12} in certain transmethylation reactions.[19] In view of these demonstrated activities of vitamin B_{12}, its inclusion in polyvitamin preparations seems reasonable. On the basis of the study here reported, it seems unlikely that quantities of vitamin B_{12} up to 100 μg. per day will have any significant effect upon the appetite of adult humans, but further studies on the effects of vitamin B_{12} in adult nutrition seem fully justified.

Summary

Two schedules of oral vitamin B_{12} supplementation, namely, 100 μg. daily for 3 months and 30 μg. three times a day for 3 months were evaluated in conjunction with a placebo given daily for 3 months. There was no significant weight gain attributable to vitamin B_{12} administration in this group of 44 healthy adult females given an *ad libitum* diet for the 12-month period encompassed by the control and treatment phases of the study.

There was no significant difference in the weight gain during the period when the patients received a daily dose of 100 μg. of vitamin B_{12} as compared with the period when they received 30 μg. three times per day.

The value of the Latin square design is emphasized as a valuable aid in the interpretation of a long-term study such as this, where a number of uncontrollable variables are involved.

Acknowledgments

We wish to express our appreciation to Mr. Joseph L. Ciminera for his help in planning this study in a manner to facilitate statistical analysis. We would like also to acknowledge our indebtedness to Mrs. Rose Hofer, R.N., and her assistants, without whose co-operation, patience, and careful adherence to the protocol, this study would have been impossible.

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Resumen

Adición de vitamina B_{12} a la dieta de adultos sanos: un estudio de cambios de peso empleando un esquema cuadrado latino

Dos regímenes de adición de vitamina B_{12} por vía oral, es decir, 100 microgramos por día durante 3 meses, y 30 μgms. 3 veces por día durante 3 meses, se valoraron en conjunto con un placebo suministrado todos los días durante 3 meses. No se observó ningun aumento importante de peso que se podía atribuir a la administración de vitamina B_{12} en este grupo de 44 mujeres adultas sanas recibiendo una dieta *ad libitum* durante el período de 12 meses abarcado por las fases control y experimental de este estudio.

No hubo ninguna diferencia importante en el aumento de peso durante el período que los pacientes recibían una dosis diaria de 100 μgms. de la vitamina, en comparacíon con el período en que recibían 30 μgms. 3 veces por día.

Se insiste en el valor del esquema cuadrado latino como un auxilio de gran importancia en la interpretación de una investigación prolongada como ésta, en donde se encuentran factores tan variados e incontrolables.

HYPOPOTASSEMIA *in Human Starvation and Gastric Resection*

By HAL T. WILSON, M.D.* AND FENTON H. SINK, M.D.

THE CLINICAL picture of potassium ion lack is widely recognized and discussed at the present time.[1,2] We believe there may be more effects of a potassium deficiency than have been described and that they may appear after months of deprivation. Before describing our observations, a brief discussion of the causes of this deficiency is presented.

It is agreed that a reduced food intake plus normal and abnormal losses of potassium in bodily secretions underlie most instances of this syndrome. Gastrointestinal disorders, including prolonged vomiting, diarrhea of infants, the sprue syndrome, and draining fistulas have been shown to cause large potassium ion losses;[3,4] with these there is often an associated poor intake. Lowered serum potassium levels are seen in the aforementioned disorders, as well as in diabetic acidosis, alkalosis of Cushing's disease or desoxycorticosterone intoxication, and in familial periodic paralysis. In addition to potassium deprivation and unusual loss, there is the constant urinary loss which is obligatory and may amount to 1.5 to 3 Gm. daily even during fasting.[1,5,6,8]

The usual symptoms of potassium lack are: listlessness, muscular weakness of the extremities, dyspnea and gasping respirations, abdominal distention, and ultimately paralysis of both skeletal and cardiac muscle.[2]

It seems inevitable that prolonged starvation alone should produce hypopotassemia. Amatuzio[7] found low serum potassium levels in cirrhotics who had had an inadequate food intake for 4 to 6 months. Danowski[3] mentions anorexia nervosa as another possible cause. Recently we have seen three patients who developed severe potassium deficiency entirely on the basis of starvation, or starvation with a poorly functioning gastric resection. Our patients presented several unusual features.

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CASE REPORTS

Case 1

The first case reported is that of a patient who voluntarily starved six months and lost 50 pounds; the resulting weakness and apparent psychotic state were associated with hypopotassemia. Correction of the low serum level paralleled her recovery.

Mrs. M. B., a 55-year-old white woman, entered the hospital on August 11, 1951, so weak and irrational that a history was necessarily obtained from her family and later verified by the patient. Because of fear of cancer, for six months prior to admission to the hospital she had eaten a diet consisting only of grapes and grape juice in order to avoid the many other types of food which she imagined were injurious. Although she felt that her peculiar diet had relieved this distress, she had lost 50 pounds of weight since the beginning of her deprivation, and her strength had gradually ebbed, so that for five weeks she had been bedridden.

The patient was a malnourished and dehydrated white woman with deeply pigmented skin, who weighed 95 pounds. She was weak and irrational. The blood pressure was 92/60 mm., pulse 92 and regular, and respirations 16 per minute. Examination of the head, mucous membranes, neck, and heart and lungs

were within normal limits. There was a midline abdominal scar but no other abnormalities. Fundus and adnexae were not palpable; there were black feces in the rectum. The skin was gray-brown over the entire body except the palms and soles; skin creases were darkened. The reflexes were hypoactive and the knee jerks and ankle jerks were absent. There was a questionable Babinski sign on the left. Muscle strength was generally diminished, more so on the left side.

The patient's course during her first weeks in the hospital was marked by weakness and variable mental aberrations. It should be emphasized that, because of her extreme weakness, she was unable to feed herself or even to turn herself in bed. Her mental symptoms took the forms of melancholia, hallucinations, and occasional euphoria. The initial clinical impression was that starvation was the most likely cause of her illness, but Addison's disease and carcinoma with cachexia were considered.

Repeated determinations of the CO_2 combining power during the first three days of her hospitalization consistently showed levels above 80 volumes per cent. (The county hospital laboratory colorimetric determinations were not accurate above 80 volumes per cent.) The nonprotein nitrogen was 37 mg. per 100 cc. and two blood sugars were 125 mg. per 100 cc. and 128 mg. per 100 cc. Urinalyses were normal. Hemoglobin was 10 Gm. per 100 cc. Wasserman and Kahn serologic tests were negative. Serum calcium, phosphorus and chlorides, bromsulphalein excretion, total proteins, A/G ratio, and spinal fluid tests were normal. Samples of hair, nails, and urine were negative for arsenic. Gastric analysis, ACTH-eosinophil test, and Kepler water tests were all within normal limits. Stools were negative for occult blood. Chest fluoroscopy and x-ray, skull x-ray, upper gastrointestinal series, and oral cholecystogram were all normal.

An electrocardiogram taken two days after admission showed depressed ST segments, low T waves, and prolonged QT intervals (Fig. 1). The blood pressure persisted at levels of 80–90 mm. systolic and 50–70 mm. diastolic.

Because of the patient's severe dehydration and malnutrition, she was first treated with intravenous fluids consisting chiefly of 5 per cent glucose in water and sodium chloride. Although she seemed slightly more alert following these hydration measures, her mental status and physical weakness remained abnormal. She had multiple complaints of a bizarre nature, including chills and sweating without a temperature variation, afternoon leg cramps, sudden losses of vision without opthalmologic evidence of disease, and marked emotional lability.

It was the opinion of the staff, and concurred in by the psychiatrist, that involutional melancholia was the most likely diagnosis, and that commitment to a mental institution for electroshock therapy was indicated. Neurological examination now revealed hypoactivity of tendon reflexes of the upper extremities with absent ankle and knee jerks, but with active ankle and patellar clonus. The Babinski sign was definitely present on the left. There was generalized muscular weakness and flaccidity. Inco-ordination was greater on the left side.

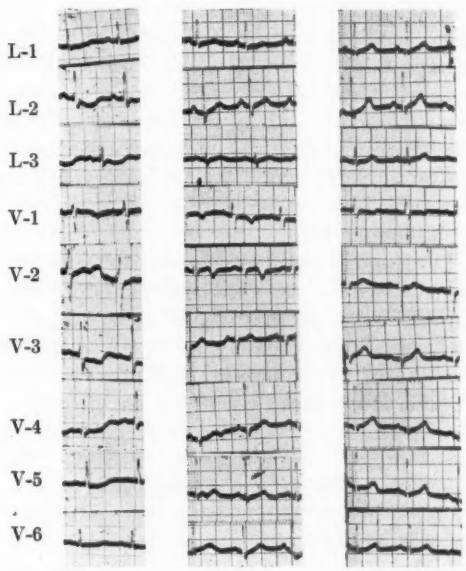

Fig. 1. M. B.

A serum potassium taken one day after admission was reported on August 15, 1951, as 12 mg. per 100 cc. (3.1 mEq./L.) in a hemolyzed specimen. The sodium was 354 mg. per 100 cc. (154 mEq./L.). In spite of this and the signs of low potassium on the electrocardiogram, only 1 liter of KCl (2 Gm.) was given. For the subsequent two weeks she gained in strength, but was still disoriented and confused, and had thick speech and very poor co-ordination. Although the electrocardiogram was now nearly normal, the serum potassium on September 5, 1951, was only 9.3 mg. per 100 cc. (2.4 mEq./L.) in a well-drawn serum. Intensive therapy with potassium was now decided upon.

In addition to her diet containing approximately 5 Gm. of potassium, 800 cc. orange juice per day and 6 Gm. of potassium chloride were given by mouth every day. She received this for one week beginning Sept. 6, 1951, with remarkable subjective and objective improvement. Repeated neurological examination now showed a slight hyperactivity of all tendon reflexes, absent patellar clonus, absent abdominal reflexes, absent right but present left ankle clonus, and positive Babinski and Hoffman signs on the left side. Sensory modalities were not impaired. There still remained a general motor weakness, more marked in the left arm and the right thigh and leg. Co-ordination, by the finger to nose and heel-knee-toe tests, was impaired, more noticeably on the left side. By this time the blood pressure had gradually risen to a level of 150/100 mm. Hg.

Oral potassium was then discontinued and replaced with a one-week course of 6 Gm. KCl intravenously per day. Clinically, improvement was approximately the same as by the oral route; neurological findings were not significantly altered except for an increase in muscle strength proportionately equal to that noted during oral potassium therapy. The serum potassium taken 5 days after discontinuance of all but a general diet, revealed a level of 12.8 mg. per 100 cc. (3.3 mEq./L.); the 24-hour urine potassium output was 180 mg. per 100 cc. (47 mEq./L.) or 2.48 Gm. per 24 hours. (The normal urinary excretion of potassium is about 2 to 4 Gm. per 24 hours.)*

On the basis of clinical improvement and laboratory reports, the patient on Sept. 23, 1951, was again put on a course of oral potassium chloride in the amount of 6 Gm. per day. Both objective and subjective improvement were rapid. Electrocardiograms taken during and after potassium therapy had reverted to normal. Neurological findings became entirely normal, although slight right leg and left arm paresis persisted.

The patient had become physically able and mentally alert and was discharged from the hospital on 9 Gm. of potassium chloride daily. However, after approximately one month of this high potassium intake, the serum potassium on Oct. 15, 1951, was still only 13.8 mg. per 100 cc. (3.5 mEq./L.), and the 24-hour urine potassium was 132 mg. per 100 cc. (34 mEq./L.) or a total of 2.11 Gm. (54.4 mEq.) per day. Oral potassium was discontinued at this time. On Nov. 30, 1951, the serum level was still low, 12.9 mg. per 100 cc. (3.3 mEq./L.).

When she was last seen on Jan. 1, 1952, Mrs. M. B. had taken no extra-dietary potassium for approximately two and a half months. There had been no recurrence of symptoms. Physical examination was identical to her last hospital visit except for weight gain to 145 pounds. Her serum potassium had risen to a normal of 15.8 mg. per 100 cc. (4.1 mEq./L.).

The trace of a left hemiparesis and right leg weakness suggests that a number of cerebral focal lesions could produce these widespread central nervous system changes. However, no clearcut onset of any such accident or accidents can be elicited. This patient's almost complete recovery now emphasizes a more diffuse nervous system injury.

Case 2

Mrs. K. I., a 42-year-old woman who weighed 90 pounds and was very weak, also

*The Tisdall chemical technique as modified by Jacob and Hoffman was used in all potassium determinations. *J. Biol. Chem.* 93: 685, 1931; *Ibid.* 120: 57, 1937.

had a low serum potassium one and one half years following a gastric resection. She was first seen in May, 1952, complaining of pain in the left upper quadrant of her abdomen. She had had abdominal pains of many kinds for about 17 years. A diagnosis of duodenal ulcer had been made two years before and in October of 1951 a gastric resection was performed. Since that time she had gradually lost weight and although her burning epigastric discomfort had disappeared she had right and left upper quadrant cramping, intermittent distress, fullness, and nausea. This was always worse after eating and better after vomiting.

Physical examination showed an emaciated woman with a slightly tan skin. She weighed $90^1/_4$ pounds. The only abnormality other than emotional lability was a definite ataxia in the left arm during the finger-to-nose test. She was left-handed.

The serum potassium at this time was 11.9 mg. per 100 cc. (3 mEq./L.). For three months she continued to wax and wane, showing weight gain of a pound or two on a special feeding program and tincture of belladonna. In August 1952 she began to have more distress and was discouraged and extremely weak. The serum potassium was 12.9 mg. per 100 cc. (3.3 mEq./L.) and the electrocardiogram was normal. She was admitted to the hospital and given parenteral and oral potassium and restarted on a feeding program and tincture of belladonna. Since that time she has gained six pounds in weight, immeasurably in strength, and has returned to work. A serum potassium on Nov. 12, 1952, was 4.4 mEq./L. or 17.2 mg. per 100 cc. The left arm ataxia was gone.

Case 3

Mrs. H. J. was a woman with a weight loss of 30 pounds following a gastric resection three years before; return of low potassium levels to normal accompanied return of muscle strength and co-ordination.

She was admitted to the hospital on July 25, 1952, with a chief complaint of cramping, intermittent upper abdominal distress, and nausea. Such attacks had been present since she had had a gastric resection in 1949. She had not had vomiting or diarrhea, but had gradually eliminated one food after another from her dietary intake. She was weak, weighed only 100 pounds, and had a skin pigmentation which was brown and dappled in appearance. She also looked sallow. Her speech showed hesitancy, dysarthria, with a nasal quality, and she had great difficulty in keeping the trend of the conversation. Her vision was poor because of blurring.

There were many fine inspiratory rales throughout both lung fields. The heart rate was 80 per minute and forceful in beat, but there were no murmurs. The blood pressure was 98/68 mm. The abdomen was tympanitic and quiet; the liver was palpable in the right upper quadrant 7 cm. below the right costal margin in the right midclavicular line. It was not tender. Examination of the rectum and pelvis was normal. Reflexes were absent in all extremities. Vibratory sense was normal. There was moderate pretibial edema.

Clinical impression was that of starvation and a malfunctioning gastric resection. The serum potassium was 11.9 mg. per 100 cc. (3.3 mEq./L.), red blood cell count was 2,530,000/cu.mm., hemoglobin was 8.5 Gm. per 100 cc., and white blood cell count and differential were normal. Total serum proteins were 5 Gm. per 100 cc., and the serum bilirubin was 1.9 mg. per 100 cc. The electrocardiogram showed an increase in the interventricular conduction time and depressed T waves in limb leads 1 and 2 and in precordial leads 1, 2, 3, 4, 5, and 6 (Fig. 2).

She was treated with intravenous potassium and supportive fluids and put on a high calorie diet with frequent feedings, and therapeutic doses of vitamin B complex. The day after admission a chest x-ray showed evidence of pulmonary edema. Later, upper gastrointestinal, gallbladder, and barium enema x-rays were normal. Gastric analysis showed achlorhydria to histamine. She improved steadily in strength, her chest cleared on the third day, and by the tenth day her chest was clear to x-ray; the heart was smaller in size, and the electrocardiogram had significantly improved. She went home on the twelfth day after ad-

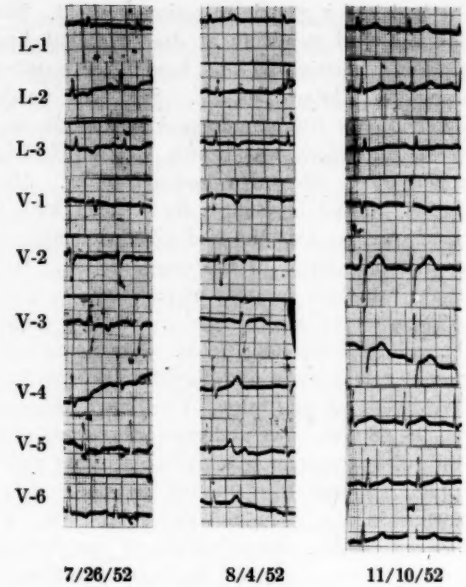

Fig. 2. H. J.

mission, and continued to gain in weight and strength.

Three months later, Oct. 29, 1952, her serum potassium was 4.4 mEq./L. and she had gained 15 pounds. The dysarthria, the hesitation in speech, forgetfulness, and the blurring of vision had all disappeared. The electrocardiogram taken on Nov. 10, 1952 was entirely normal.

Discussion

It seems clear that these are cases of hypopotassemia and that the body tissues suffered prolonged potassium lack. The presence of alkalosis in *Case 1* is corroboratory.[1] In this case, avidity of the tissues for potassium is shown by the sustained low serum levels of this ion and by the fact that there was no increased urinary potassium output in the face of large amounts of oral and parenteral potassium salts.[5]

Darrow[1] says, "Under abnormal conditions as much as one half of the intracellular potassium may be replaced by two thirds of the equivalent amount of sodium." The removal of intracellular sodium and the return of potassium to the cells is not a rapid process. According to Darrow,[1] "Deficits may be so large that they cannot be restored parenterally for 6 days because administration of more potassium does not restore all deficits more rapidly." Furthermore, Tarail[5] found only one of his hypopotassemia patients in positive potassium balance after treatment. The period of potassium feeding was too brief (8 days) in the others.

In our patients, generalized muscular weakness and hyporeflexia, although long lasting and slow to disappear, seem akin to what is seen in more acute deprivation. The mental slowness, dysarthria, emotional lability, and disorientation have been mentioned before in the literature on starvation.[9] Thiamine and niacin deficiencies are associated with well-recognized neurological changes. In *Case 1* clearing of the sensorium and return of muscle strength and reflexes coincided with potassium administration, but were not affected by two weeks of feeding alone. Extradietary vitamins were not used in *Case 1*. Thiamine, riboflavin, and niacin in therapeutic doses (at least 50 mg. thiamine, 25 mg. riboflavin, 200 mg. niacin, and vitamin C daily *per os* or intravenously) were given in *Cases 2* and *3*.

Perhaps the neurological abnormalities often observed during starvation are in part related to hypopotassemia. A prolonged mild deficiency of potassium seems as likely to produce damage to nerve tissues as an acute severe lack of the electrolyte. The usual treatment of starvation includes replacement by calories and vitamins and the effect of individual mineral replacements may be obscured. Certainly, more study of this point is clearly indicated.

Conclusions

Three cases of long-standing starvation and resultant potassium deficiency are presented. Potassium deficiency may be a frequent feature of starvation. Many signs of central nervous system damage were recorded and observed to disappear with treatment by food, vitamins, and potassium salts. A tremendous dose (261 Gm. or 3400 mEq.) of KCl in addition to a high potassium diet was given to one

patient over a period of one and half months.* Restoration of intracellular potassium may be slow in such cases. It is possible that many of the central nervous system changes in starvation are due to intracellular potassium deficit.

*261 Gm. of KCl furnishes about 136 Gm. of potassium. During the $3^1/_2$ months of observation the daily urinary losses would equal between 2 and $2^1/_2$ Gm. per day or at least 225 Gm. of potassium all told. Therefore, extradietary potassium during this time was not sufficient to replace urinary losses and tissue reserves had to be built up from food.

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Resumen

Hipopotasemia en la inanición humana y en la resección gástrica

Se presentan tres casos de hiponutrición prolongada y de resultante hipopotasemia. La hipopotasemia puede ser un hecho frecuente en la inanición. Muchos signos de lesiones en el sistema nervioso central se han observado que han desaparecido al ser tratados con alimentación, vitaminas, y sales de potasio. Una dosis masiva (261 gms. o 3400 miliequivalentes) de KCl, sobreañadida a una dieta rica en potasio, se administró a un paciente durante un período de $1^1/_2$ meses. La restauración del potasio intracelular puede ser lenta en tales casos. Es posible que muchos de los cambios que se observan en el sistema nervioso central durante la inanición sean debidos a un déficit de potasio intracelular.

POSTHEPATITIS SYNDROME

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With the technical assistance of Susana Riqueros, María Josefina Besa, Mercedes Cuevas, Lucy Cuevas, Mercedes Navarro, and Sylvia Olmedo

FOR MANY YEARS it has been known that some patients do not completely recover after the acute phase of hepatitis. The transition from the first episode to a chronic hepatic process was pointed out by Ehrström[1] and Bloomfield,[2] and we[3] have observed this course repeatedly. Polak[4] and Rennie[5] have reported cases of cirrhosis following acute hepatitis.

However, a great number of cases of hepatitis do not progress to a clinically detectable chronic form, but present varied subjective and objective abnormalities, among which dyspepsia is the most frequent. This association of signs and symptoms is known as *the posthepatitis syndrome* (Caravatti[6]). Some investigators[7,8] on the basis of the bilirubin excretion test, think that the hepatic damage determined by an attack of hepatitis might be permanent. However, Lucké[9] has studied the livers of 14 persons who had recovered from an attack of hepatitis from one week to 14 months before and who died of unrelated causes. He found a complete restoration of the hepatic parenchyma.

The study of 200 individuals with prolonged convalescence after postvaccinal (yellow fever) hepatitis led Benjamin and Hoyt[10] to conclude that only a small number present a residual damage. The only objective evidence of liver disease was afforded by the bromsulphalein test which showed abnormal results in 32 per cent of the cases. Fishman[11] found important residual symptoms in 30 out of 602 individuals convalescing from hepatitis; nevertheless, bromsulphalein retention was always normal.

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A large group of patients who failed to recover promptly after an attack of hepatitis was studied by Barker and associates.[12] They believe that the signs and symptoms of these patients are due to a residual hepatic dysfunction and call the syndrome "chronic hepatitis."

During the convalescent stage of experimental hepatitis, Neefe and Reinhold[13] often found abnormal laboratory tests which took variable periods of time to return to normal. Neefe[14] has reported 4 cases of chronic hepatitis following an experimentally induced acute episode; in spite of the persistence of symptoms and histological abnormality in these cases, the commonly used laboratory tests did not reveal any evidence of hepatic disturbance.

Cases of prolonged hepatitis without important functional or histological abnormalities have been studied by Watson and Hoffbauer;[15] these cases generally progress to cirrhosis.

Twenty patients, observed by Sherlock and Walshe,[16] developed fatigue and gastrointestinal symptoms, usually with hepatomegaly, following an attack of acute hepatitis. All the hepatic tests performed, including bromsulphalein, and the histological picture of biopsy specimens were normal. These results were similar to those obtained in subjects who had recovered from acute hepatitis and were symptom-free.

Klatskin and Rappaport[17] found symptoms referable to the liver, hepatomegaly or evidence of hepatic dysfunction, for periods up to 27 years in about half of 217 cases of presumably cured acute hepatitis. In this series, the number of convalescent subjects was small, as only 32 had their icteric episode during the 4 months previous to the study.

Barker and Capps[18] commented on the difficulty of distinguishing between residual symptoms of acute hepatitis and other digestive diseases. Flood and James[19] have studied 37 patients in whom evidences of disease persisted for over two months after the initial symptoms; the bromsulphalein test generally gave pathological results and the liver biopsies showed periportal infiltration. Complete recovery was observed in this group after periods from 73 to 578 days.

The course of 78 patients with delayed convalescence after acute hepatitis was followed by Marion.[20] In 44 per cent of the group, complete objective and subjective recovery was observed; in a similar proportion, symptoms disappeared but signs continued to be present; and in 8 per cent, although laboratory tests returned to normal, subjective complaints remained.

Neefe and associates[21] obtained specimens of feces and liver tissue by biopsy from three of their patients with persistent symptoms after experimental hepatitis; a suspension of these materials was given to volunteers, who developed an anicteric disease which could be interpreted as hepatitis.

In 60 out of 350 hepatitis patients, Kunkel *et al.*[22] observed delayed convalescence; 47 recovered, 2 progressed to a chronic form of the disease, 4 presented a prolonged abnormal bromsulphalein retention, and 7, a persistent hyperbilirubinemia. Eight patients (2.3 per cent of the total) did not completely recover after more than one year's time.

Volwiler and Elliott[23] note that it is hard to differentiate true chronic hepatitis from the posthepatitis syndrome in which laboratory tests and liver histology are normal. The importance of this differentiation is also stressed by Havens and Ginder.[24] Brick[25] commented on the distinguishing features between the posthepatitis syndrome and posthepatitis cirrhosis, and states that it may be impossible to establish the relative proportion of both forms.

Tumen and Cohn[26] found one or more abnormal laboratory tests in 21 individuals who had hepatitis from 6 months to 10 years before; 5 had symptoms and 7 hepatomegaly, but these abnormalities were unrelated to the laboratory results. They think that the prognostic significance of the tests can only be judged by a repeated study.

Gardner and associates[27] studied 114 individuals who had been hospitalized for acute hepatitis from 6 months to one year previously; 46 had been discharged with slight residual abnormalities, and 68 as presumably cured. They found no significant differences between the two groups. Hult[28] described a clinical picture which follows acute hepatitis and which is characterized by certain symptoms: normal or only slightly elevated bilirubinemia, normal liver tests, and lack of infiltration and fibrosis in the histological study of liver biopsy. Koszalka *et al.*[29] and Armas and associates[30] also observed cases of chronic or recurrent hepatitis.

Material and Methods

One hundred and twenty-five cases of acute hepatitis have been subjected to periodic examinations from the icteric episode up to 20 months later. The age and sex distributions and the duration of jaundice are tabulated in Table I.

TABLE I

Material

Number of cases:	Males, 94	Females, 31	Total, 125
Age			
10–20 years			27
21–30 "			55
31–40 "			22
41–50 "			14
51–60 "			6
61 or more			1
Duration of jaundice			
Undetermined			11
Less than 30 days			44
31–60 "			63
61–90 "			7

In 56 patients, intravenous injections had been given at a time compatible with the length of the incubation period of inoculation hepatitis.

In every examination a careful search was made for residual dyspepsia and for signs which could be related to the original disease.

At the same time, a routine laboratory study was performed; this included prompt direct[31] and total[32] serum bilirubin and flocculation reactions (cephalin-cholesterol,[33] colloidal red,[34] thymol,[35,36] zinc,[37] phenol,[38] and Takata[39]).

In those cases in which dyspepsia was present, its relation to the icteric episode was carefully noted, and complementary laboratory examinations were performed in order to rule out a concomitant disease. Those individuals who in the first examination had clinical or laboratory abnormalities were repeatedly studied.

Results

The number of individuals who were examined for the first time and those who were found normal on each monthly period, are shown in Table II.

TABLE II

Individuals Examined for the First Time and Number of Those Found Normal on Each Monthly Period

Months	1	2	3	4	5	6	7	8	9	10	11	12	13–20	Total
Examined	62	20	13	15	6	1	3	1	1	0	1	1	1	125
Normals	7	4	6	9	1	1	2	0	1	0	1	0	1	33

TABLE III

Cumulative Number of Individuals Who Showed Abnormal Findings at Each Examination and Number of Those Who Were Found Normal

Months	1	2	3	4	5	6	7	8	9	10	11	12	13–20	Total
Abnormal	55	63	67	54	54	53	47	44	43	41	44	44	48	657
Normal		8	3	9	5	1	7	4	1	3	0	1	2	44

In Table III the number of individuals who showed abnormal findings is expressed cumulatively for each monthly period; it is logical to assume that those who in a certain month presented abnormalities also would have shown them during the previous ones. The number of those who were found normal is also given.

The analysis of these tables shows that 77 individuals (33 found normal at the first examination and 44 who reverted to normal at the following ones) completely recovered, both clinically and chemically, during the observation period. In five others a calculous gallbladder was revealed by x-ray; seven had gastrointestinal symptoms previous to the icteric episode which were not influenced by the hepatitis, and in three a definite extrahepatic cause accounted for the abnormalities found.

A total of 92 individuals were thus obtained in whom a careful study revealed complete normality (77) or extrahepatic disease (15).

To these 92 cases we must add 2 who were subjected to a more complete study, including liver biopsy, in order to obtain information. They were free of symptoms and even the most sensitive tests showed normal results. One of them had a normal hepatic histology three months after the icteric episode (Fig. 1) and the other one, slight proliferation of fibrous tissue in the portal spaces, four months after the acute illness (Fig. 2).

At the last examination (2 to 20 months after the icteric episode), the remaining 31 individuals showed a clinical and/or laboratory abnormality, and in 19 a complete study could be performed. This study included, besides the routine tests mentioned above, bromsulphalein,[40] twenty-four hour urobilinogen,[41] total urinary coproporphyrin,[42] serum proteins,[43] prothrombin,[44] cholecystography, and liver biopsy.[45]

In Table IV the results obtained with these tests on each case are tabulated, together with the clinical abnormality which justified the complete study.

These results are summarized in Table V. They demonstrate that at the time of performing the complementary study, the most frequent disturbance was dyspepsia. It is interesting to note that the flocculation reactions

TABLE IV

Study of 19 Hepatitis Cases Who Showed an Abnormality of the Routine Laboratory Investigation in the Last Examination

Name	Months after acute episode	Clinical disturbance	Flocculation reactions	Bilirubin 1 min. (mg./100cc.serum)	Bilirubin total (mg./100cc.serum)	Bromsulphalein (% retention in 30 minutes)	Urine urobilinogen (mg. in 24 hours)	Urine coproporphyrin (mg. in 24 hours)	Albumin (gm./100cc.serum)	Globulin (gm./100cc.serum)	Prothrombin (%)	Cholecystography	Liver biopsy
E. G.	3	Dyspepsia	Pos.	N.	N.	4	—	—	—	—	—	—	Abnormal
F. L.	4	Dyspepsia and hepatomegaly	Neg.	N.	N.	2	0.28	107	3.8	3.08	100	Normal	Abnormal
J. C.	7	—	Pos.	N.	N.	9	1.7	136.2	4.06	3.75	100	—	Normal
S. S.	6	Dyspepsia	Neg.	N.	N.	4	0.7	210	3.80	3	100	Normal	Abnormal
C. O.	7	Recurrent jaundice	Neg.	N.	N.	4	1.0	45	4.45	2.45	100	Normal	Normal
J. L.	4	Dyspepsia	Pos.	N.	N.	0.5	—	—	3.97	3.75	—	—	Normal
G. R.	4	Dyspepsia	Neg.	N.	N.	6	—	285.2	4.15	3.48	56	Faint shadow	—
R. B.	5	Dyspepsia and hepatomegaly	Neg.	N.	N.	3.5	1.15	180	4.30	3.20	100	Nonvisualized	Abnormal
J. O.	4	Dyspepsia and hepatomegaly	Neg.	N.	N.	5	0.6	113	4.76	2.95	100	—	—
R. J.	3	Dyspepsia	Pos.	N.	N.	9.5	0.78	—	—	—	100	Normal	Abnormal
H. L.	5	Dyspepsia	Neg.	N.	N.	4	1.5	113.4	3.97	3.33	85	Normal	Normal
H. R.	2	Dyspepsia and hepatomegaly	Neg.	N.	N.	7.5	—	—	—	—	—	—	Abnormal
R. D.	4	Dyspepsia and hepatomegaly	Neg.	N.	N.	6	1.5	73.9	6.15	1.5	100	Normal	Normal
J. Z.	4	Dyspepsia	Neg.	A.	A.	5	2.5	868	—	—	45	Normal	Abnormal
M. A.	9	Dyspepsia	Neg.	N.	N.	8	2.4	190	3.3	3.7	100	Previous cholecystectomy	Normal
E. P.	5	Dyspepsia and hepatomegaly	Pos.	N.	N.	3	—	—	4	3	—	Faint shadow	Normal
E. V.	7	Dyspepsia and hepatomegaly	Neg.	N.	N.	2	0.77	192.5	4.17	3.28	100	Normal	Normal
J. M.	6	Dyspepsia and hepatomegaly	Neg.	N.	N.	6	—	—	4.5	2.5	40	Normal	Abnormal
E. S.	3	Dyspepsia	Neg.	N.	N.	7	0.69	57.6	4.67	3.02	—	Nonvisualized	Abnormal

Pos. = positive. Neg. = negative. N. = normal. A. = abnormal.

TABLE V

Study of 19 Hepatitis Cases Who Showed an Abnormality of the Routine Laboratory Investigation in the Last Examination

Clinical disturbance:	
Dyspepsia	9
Dyspepsia and hepatomegaly	8
Transient icteric episodes	1
None	1
Flocculation reactions:	
Positive	5
Negative	14
Total bilirubin:	
Elevated	1
Normal	18
One minute bilirubin:	
Elevated	1
Normal	18
Bromsulphalein:	
Normal	19
24 hours urine urobilinogen:	
Performed in	13
Normal	13
24 hours urine coproporphyrin:	
Performed in	13
Abnormal	6
Normal	6
Albumin:	
Performed in	15
Normal	15
Globulin:	
Performed in	15
Normal	15
Prothrombin:	
Performed in	14
Abnormal	4
Normal	10
Cholecystography:	
Performed in	13
Faint shadow	2
Nonvisualized	2
Normal	9
Liver biopsy:	
Performed in	17
Abnormal	9
Normal	8

were positive in only 5 individuals, and prompt and total bilirubins elevated in only one; bromsulphalein and twenty-four hour urobilinogen were regularly normal. The laboratory test which gave a higher percentage of abnormal results was, in agreement with the studies of Watson and associates,[46] the urine total coproporphyrin.

Liver biopsy was performed in 17 of the 19 individuals with a complete laboratory study; in 8, hepatic histology was normal. The reports on 5 of the 9 abnormal biopsies were as follows:

E. G., Man, 27 years of age. Biopsy three months after the acute episode. Normal lobular and trabecular architectures; normal liver cells. Slight increase of fibrous tissue and of cellularity in the portal spaces. The intertrabecular reticulum appears stained with eosin.

F. L., Woman, 23 years of age. Biopsy four months after the acute episode. Normal lobular and trabecular architecture. Mild increase of fibrous tissue in the portal spaces. Inflammatory reaction is absent.

S. S., Woman, 22 years of age. Biopsy six months after the acute episode. Normal lobular architecture. Infiltration with large mononuclears and fibroblasts and slight formation of collagenous fibers in the portal spaces. Normal liver cells with no fat.

H. R., Man, 58 years of age. Biopsy two months after the acute episode. Normal lobular architecture. Infiltration with fibroblasts and a few round cells in the portal spaces where some fibers are differentiated. The interlobular reticulum appears stained with eosin.

E. S., Woman, 23 years of age. Biopsy three months after the acute episode. Normal lobular and trabecular architecture. Slight cellular and collagenous proliferation in the portal spaces. A few focci of inflammatory infiltration, especially with round cells and large macrophages.

The histological pictures of the other four cases are shown in Figures 3 to 8.

Discussion

The prolonged and repeated study of 125 patients with hepatitis observed during the acute episode and for a variable consecutive period, has shown that 31 had a residual picture closely related to the fundamental disease.

It is not possible to ascertain the prognostic significance of the residual disturbance in these cases. In some of our patients the abnormalities previously shown disappeared only after more than 6 months following the acute episode. This is why residual disturbance

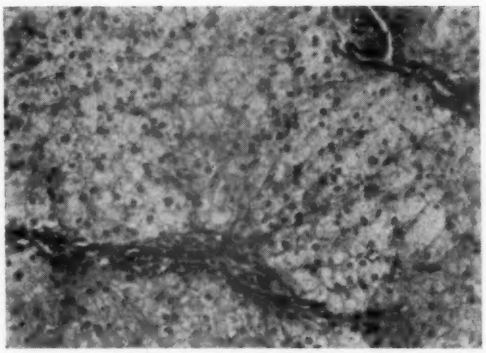

Fig. 1. C. M.—Man of 20 years of age. Photomicrograph of liver tissue obtained by punch biopsy three months after the acute episode. van Gieson. Normal lobular and trabecular architectures. Normal parenchymal cells.

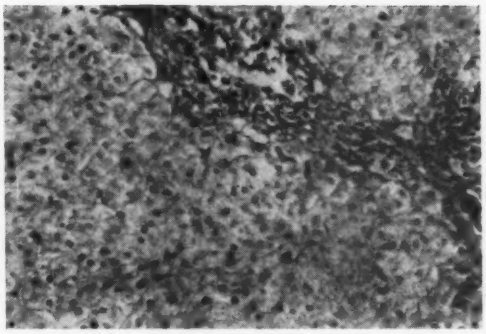

Fig. 2. H. R.—Man of 34 years of age. Photomicrograph of liver tissue obtained by punch biopsy four months after the acute episode. van Gieson. Normal lobular and trabecular architectures. Slight macrophage proliferation in the portal spaces, where fibrous tissue is definitely increased and tends to partially surround the lobules.

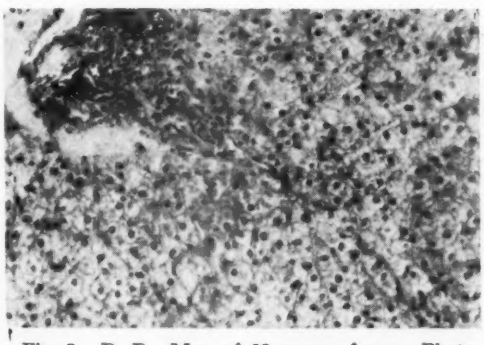

Fig. 3. R. B.—Man of 28 years of age. Photomicrograph of liver tissue obtained by punch biopsy 5 months after the acute episode. van Gieson. Exaggerated lobular architecture. Round cell and fibrous tissue proliferations in the portal spaces.

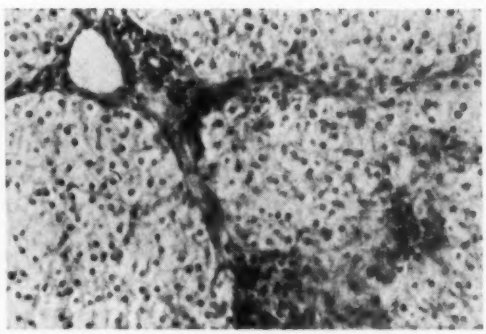

Fig. 4. R. J.—Man of 21 years. Photomicrograph of liver tissue obtained by punch biopsy 3 months after the acute episode. van Gieson. Normal lobular and trabecular architectures. The portal spaces are clearly shown due to increase of round and fusiform cells especially around the portal vein and the small ducts; slight differentiation of collagenous fibers.

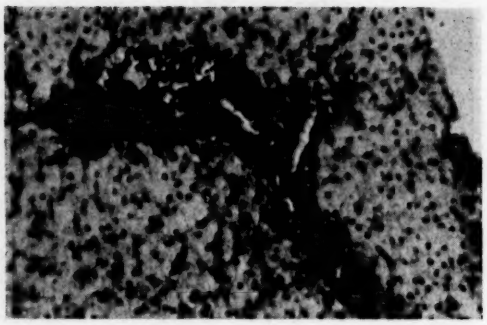

Fig. 5. J. Z.—Man of 22 years. Photomicrograph of liver tissue obtained by punch biopsy four months after the acute episode. van Gieson. Normal lobular and trabecular architectures. Normal parenchymal cells. The intertrabecular fibers show perivascular infiltration with round and fusiform cells and proliferation of fibrous tissue. No fat.

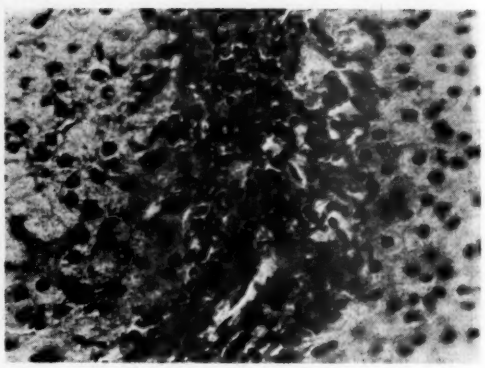

Fig. 6. Same as Fig. 5. Portal space.

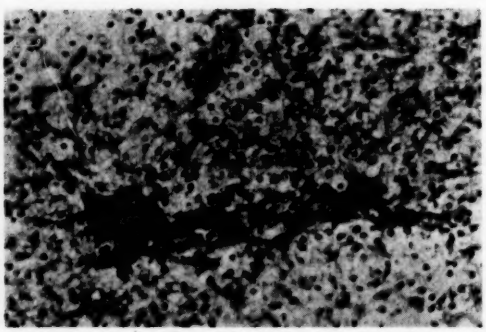

Fig. 7. J. M.—Woman of 28 years. Photomicrographs of liver tissue obtained by punch biopsy six months after the acute episode. H.-E. Normal lobular and trabecular architectures. Normal parenchymal cells. Marked proliferation of cells of fibroblastic type and infiltration with small and large round cells in the portal spaces.

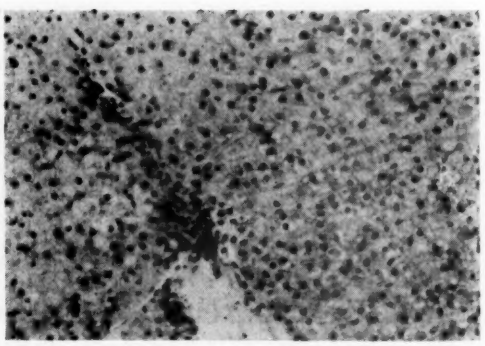

Fig. 8. J. M.—Photomicrograph of liver tissue obtained by punch biopsy three months after the one shown in Fig. 7. van Gieson. Normal liver architecture. Slight proliferation of fusiform cells in the portal spaces.

refers only to the time when the results of the study were considered. This residual disturbance may completely disappear at a later date.

Nevertheless, our study clearly shows that a significant number of hepatitis patients have important digestive symptoms for a long period of time following the acute episode. This clinical disturbance has not regularly been supported by objective data in our material. It is important to note that bromsulphalein retention was normal in all 19 individuals with residual disturbance in which this test could be carried out. The most frequent objective abnormalities were the increase in total urinary coproporphyrin and the disturbed liver histology. Accordingly, patients who do not completely recover after an acute attack of hepatitis should be subjected to repeated re-examinations for a long period of time.

Summary and Conclusions

One hundred and twenty-five individuals with acute hepatitis have been repeatedly studied, both from the clinical and laboratory points of view, from the icteric episode up to 20 months following it.

During the observation period, 77 individuals regained complete health. In five, a calculous cholecystopathy was demonstrated by x-ray examination; in 7, gastrointestinal disturbances were present before the icteric episode and were not influenced by it; and in 3, a clear cut extra-hepatic cause was discovered. One of two individuals who had no symptoms but who were completely studied in order to gain information, showed normal laboratory tests and normal liver histology. A total of 93 individuals had no residual disturbance related to the attack of hepatitis.

In the last examination (2 to 20 months after the icteric episode), 31 individuals showed a clinical and/or laboratory abnormality, and in 19 a complete study could be performed. The analysis of the results obtained in this last group demonstrates that only in a minority of cases were objective data found which could account for the residual digestive symptoms which are common after acute hepatitis.

The most frequent objective abnormalities were the increase in total urinary coproporphyrin and the altered histological picture.

A complete return to normal after an attack of acute hepatitis may take long and variable periods. This makes it impossible to ascertain the prognostic significance of a subjective or objective disturbance shown at a particular moment by patients who have had hepatitis.

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Resumen

Síndrome post-hepatitis

Se estudian en forma periódica desde el punto de vista clínico y de laboratorio 125 casos de hepatitis aguda, a partir del período ictérico y hasta un plazo máximo de 20 meses.

Durante el período de observación, 77 sujetos se normalizaron completamente. Además 5 presentaban una colecistopatía calculosa comprobada radiológicamente; 7, dispepsia que existía con anterioridad al episodio ictérico y que no se influenció con la hepatitis; y 3, una causa extra-hepática clara de su anormalidad. Uno de dos sujetos estudiados en forma completa para adquirir información reveló también normalidad completa. Esto nos da un total de 93 individuos sin perturbación residual relacionada con la hepatitis aguda.

Trienta y un individuos tenían en el último control practicado una alteración clínica o de laboratorio que justificaba un estudio más completo; 19 de ellos pudieron ser satisfactoriamente investigados.

El análisis de los resultados obtenidos en este último grupo demuestra que la frecuente dispepsia residual post-hepatitis tiene un substrato objectivo sólo en una minoría de casos y que él se traduce con una cierta mayor frecuencia por una elevación de la coproporfirina urinaria total y una anormalidad histológica hepática.

El hecho que la normalización completa después de una hepatitis aguda se alcance en períodos variables y muchas veces prolongados, hace imposible precisar la repercusión pronóstica de una perturbación subjetiva u objectiva pesquisada en un momento determinado.

Clinical Correlations in GERIATRIC NUTRITION

By JOSEPH T. FREEMAN, M.D.*

GERIATRIC nutrition is concerned primarily *but not exclusively* with two questions: (1) What diet, begun in earlier years and modified with the changing body, is conducive to a long and healthier life? (2) What should be the diet of those already old? We shall consider some of the interrelated metabolic forces in the aged which enter into the ultimate dietetic formulary for this group.

At least five factors must be evaluated: (1) anatomic and physiologic properties of the older gastrointestinal system; (2) aging modifications of biochemical balances; (3) the nature and extent of pathologic states; (4) the degree of physical activity; (5) the food intake.

In view of such factors, a proper plan of nutrition in geriatrics cannot be divorced from physiologic principles, nor can it serve as a substitute for them.

For the proper determination of dietetic needs, the morphologic and physiologic properties of the gastrointestinal system must be evaluated for each stage of life, and the effects of concurrent disease states must also be assessed.

On a somatic basis, it is doubtful whether major modifications in the diet have to be made. Despite reduction in the tone and volume of voluntary muscles with increasing age, smooth muscle maintains a sufficient degree of integrity.[1] Gastrointestinal motility is adequate for the mechanical management of the average diet[2] and gastric emptying and total digestive passage time are essentially unchanged.[3] However, the physical limitations of abdominal wall relaxation, omental fat accumulations, venous stasis, intestinal arterial atherosclerosis, and esophageal hiatal herniation, among other changes, can influence adversely the activities of otherwise efficient digestive organs.

The colon has been misused in many ways, medically and surgically, despite its important role in water balance, salt absorption, calcium metabolism, chemo-dynamics, vitamin synthesis, and digestive resorption. Most of the trauma has been directed to only one of its functions, the eliminative, without consideration for the others. Constipation is not a normal accompaniment of older age; it is either a habit carried over many years, or, if recent, it may have diagnostic significance.

Aside from adjustments for a modified appetite and reduced hunger contractions, few compensations in the diet due to *morphologic* failure alone are necessary, even in the high years.

The *physiologic* properties of the digestive channel likewise are fairly well preserved by a system of compensations. There is a reduction in the resting and stimulated volume of saliva, with a sharp drop in ptyalin content, a rise in its mucous fraction, and a drop in the serous fraction, resulting in increased viscosity.[4] Buccal starch digestion is reduced, the food mass is liquefied less easily, and more effort is placed on compensating muscles and enzymes without compromising capabilities.

The ability of the older stomach to produce free and total acids is diminished, both relatively and absolutely. In somewhat less than one-third of older persons there is no hydrochloric acid in the resting stomach, and in about an equal number there is an acid response only to specific stimulation. There is also an increase in the mucous content and leukocytes of the gastric secretions.

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The concentration of pepsin begins to diminish at about age 40, dropping slowly with increasing age. Trypsin production in the resting state drops similarly but the older pancreas is able to respond to stimulation in a manner comparable to the gland of mid-maturity. On the other hand, lipase production, before or after stimulation, is lower in old age. This is an absolute functional loss without obvious compensation. Aside from its importance in the digestive and absorptive cycles, this enzyme may be associated with steroid metabolism. Pancreatic amylase in the stimulated phase is sufficient for average digestion and to compensate for the reduction in salivary amylase.[5–8]

From these studies it may be concluded that enzymes regulating carbohydrate metabolism are able to respond to stimulation and are adequate in the older individual; those agents essential for protein absorption are somewhat reduced but sufficient in average ranges; while the mechanisms of fat digestion are modified, certain end-results of its metabolism being seen in many of the normal and abnormal phases in aging.[9]

Based on these anatomic and physiologic properties of the older digestive system alone, certain conclusions are indicated. The *physical* character of the meal and its alterations through the digestive tract up to completion of all phases of digestion should be modified to individual experience and need not be changed to accord to any fixed plan for the older age group. The *chemical* character of the diet is satisfactory as regards proteins and carbohydrates, while fats are absorbed less readily. Assuming a diet that is not grossly unbalanced, reduction in the size of meals, and better spacing of intake are sufficient adjustments for efficient absorption without resorting to extreme change.

Biochemical Balance

A second evaluation of the older age nutritional status is the quantitative determination of blood chemical levels at rest, and during food absorption, transport, and utilization.

With few exceptions, the resting and fasting levels of various components in the blood of the older body compare favorably with those of the younger person. They show the chemical balances eventually attained by the older body. These figures are arrested glimpses of processes in flux. Although a reflection of the total success or failure of complex chemical adjustments, they do not in themselves show what must be done to maintain levels essential for normal functioning, since the blood levels are resultants of the interaction of many physiologic activities.

Fasting levels of many blood components fall well within the range of normal for all ages. Carbohydrate stress tests in various glucose tolerance procedures in older subjects show that fasting blood levels are normal, but often they rise to higher ranges during the test, and take longer to return to a base line. "The increasing prevalence of delayed return and mild diabetic curves and the continual diminution of normal curves seem to represent a constant feature in the carbohydrate metabolism of older people. It also suggests a progressive lowering of the glucose tolerance during the process of aging."[10] This lessening of tolerance is not marked. If a higher, wider physiologic time curve is normal for older years, there is very little impairment of this particular absorptive function that cannot be remedied by lessening the load, lengthening the interval in administration, or both. Mosenthal[11] says that muscle mass and tone, in addition to the digestive enzymes, must be considered in the altered glucose tolerance seen in higher years.

The average fasting blood cholesterol level for mixed older age groups in one study was 214 mg. per 100 cc., males averaging 196 mg., and females 237 mg. per 100 cc.[12] These are interesting figures. In the first place, they are somewhat higher than in younger persons. Secondly, in association with other evidence of modified fat metabolism, the higher levels suggest a longer time-curve in fat utilization. Numerous observations of fat absorption and the clearance of fat particles from the blood have been compared with blood cholesterol levels.[13,14] Thirdly, the incidence of vascular disease in females rises rapidly after the climacterium. Prior to menopause, there is a

4:1, male to female ratio of clinical atherosclerotic vascular disease. In the high years the figures tend to be equalized, and there are some data to show that the incidence of severe blood vessel changes in older females begins to approximate that for males of the same surviving age. In view of the concepts of the relationship between blood lipids and vascular change these average blood cholesterol levels are pertinent.[15,16]

Total serum protein levels are slightly lower in the older ages; the lower albumin fraction, in particular, accounts for the difference. In both sexes the globulin fraction rises somewhat, but not enough to compensate for the drop in albumin.[17] Fractionation of the serum proteins by chemical and electrophoretic means has shown no characteristic pattern due to age alone.[18] Measurements of fasting levels of various end-products such as uric acid and blood urea nitrogen in the blood and urine lead to the same conclusion.[19] Correction of protein depletion in the older patient requires a greater protein intake over a longer period of time; within limits, a heightened intake is well-tolerated.[20]

Fasting calcium, phosphorus, and alkaline phosphatase levels do not change with age.[21,22]

In this discussion, it is impossible to do more than suggest the influence of the endocrine glands. The calorigenic hormones of the thyroid and adrenal glands are catabolic in character, and the hormones of the gonads and pancreas are anabolic. If disease, diet, or activity were constants, positive or negative balances could be effected by the hormone systems alone. Nitrogen and calcium retention by the androgenic substances are in complete contrast to the reverses of these states with the corticoids. The phrase "not by bread alone" may be applied to the endocrinal harmony which can promote nutritional balance.[23]

Pathologic Processes

The third conditioning circumstance in evaluating the total aspects of nutrition of the older body is consideration of its pathologic processes. These are of two types. One, like arteriosclerosis, often is an associated or adjusted change for which the body has created an equilibrium. The second, like diabetes mellitus, is more aggressive, requiring unusual efforts not only for normal activity but even for survival. Aging and surviving are the resultants of both. They affect and are affected by the nature of dietary management.

Barker has shown that the number of gastrointestinal symptoms outnumbers the incidence of intrinsic gastrointestinal diseases.[24] Cardiovascular disorders, renal and cerebral parenchymal impairment, ureteral obstructive states, psychic stresses, and mechanical modifications can initiate symptoms in the absence of lesions in the digestive system. Disconcertingly, the other side of the picture is just as deceptive. The older digestive tract can be the site of gross disease, such as ulceration, polyps (benign or undergoing neoplastic change), gallstones, diverticulitis, fistulary erosion, and even large malignancies, with few or no symptoms, or possibly with a pattern that is quite bland. The result—too many symptoms *without* gastrointestinal disease, on the one hand, and too few symptoms *with* disease, on the other—is impairment of the diagnostic value of older age gastroenterologic symptomatology.

Investigation limited strictly to these organs may fail to solve the diagnostic problem. If negative, medical search must be extended to determine which extra-digestive mechanism has given rise to the digestive disturbance. A patient may suffer a similar type of distress from gallbladder and coronary artery disease. Which is inciting the symptoms? Are these symptoms cumulative or distinctive? Are they complementary or coincidental? If both conditions are present, will relief of one affect the progress of the other? Nutritional intake must not be modified empirically on the basis of the dominance of gastrointestinal complaints.

Kountz[25] reported that the basal metabolism tends to rise parallel with the increased incidence of degenerative diseases. This quantitative measurement drops from earlier life through the middle span. As pathologic states of later life increase, there is again a rise in oxygen requirement, similar in degree to that

in the first trimester of life, though not for the same reason. These variations in oxidative reactions, their causes, and controls, have implications for the nature of the diet fitted to the life span. The number and degree of pathologic processes affect the total amount of oxidation—that is, the basal metabolic rate—related to the body's ultimate caloric needs.[26]

Primary pernicious anemia is thirty times as common in the older age group as in the 25- to 34-year group. The incidence of gastric ulcer in the 25- to 34-year-old group is only 0.7 per 100,000 compared with an incidence of 33.4 per 100,000 in the 65- to 74-year-old group. Ulcer of the duodenum has an incidence of 0.3 per 100,000 in younger ages as compared with 13.6 later. Chronic calculous cholecystitis is quite infrequent in youth, but occurs in almost 10 per cent of the older aged. Carcinoma in the gastrointestinal tract, for example, increases from 3.8 per 100,000 deaths to 211 per 100,000 deaths with rising age.[27] High as these comparative figures become with the increase in years, the numbers of gastrointestinal complaints are even higher, because of the many pathologic processes which are reflected in digestive dysfunction.

The reasons for the higher figures for diseases in the older digestive system are many. The longer a person has lived, the greater has been the exposure to infection, trauma, and psychic influences capable of producing malfunction. During a longer living span there is greater opportunity for the development of familial pathologic diatheses. The longer the life cycle, the more time has passed in which inadequate or improper nutrition has been operating to produce disturbed function or diseased tissues.

The acceptance of a digestive complaint at its face value, with therapy directed solely to the digestive organs, may be an error. The dietary plan for the older body requires a knowledge of the increased incidence of intrinsic diseases, as well as an awareness of limitations due to the effects of other pathologic changes on the digestive tract.

Nutrition, therefore, although a featured part of the gerontologic approach, cannot be used as a substitute for all its therapeutic procedures. Estimation of caloric needs based on weight and degree of activity, divided into grams of protein, fat, and carbohydrate, must be qualified by the comprehensive patterns of pathologic processes. In practice, this is a daily assignment; the patient with any illness, acute or chronic, requests dietary advice as a therapeutic measure.

Physical Activity

The relative inactivity of older age in general is comparable to a state of ineptitude or recumbency, the total effects of which are as yet unmeasured. Aspects of normality based on resting-state tests do not give a full picture of the reserves of reactive ability. Functional tests simulating normal stresses help to reveal both the weaknesses and the preserved strengths of the aging organism.

Reduced activity and increasing degenerative states are corollaries. With lessened physical activity, certain catabolic effects (reduced anabolic stimulation?) are initiated. There is evidence that such effects may be counterbalanced somewhat with the establishment of new equilibria of less destructive results.

A reduction in osteoblastic and a heightening of osteoclastic activity are associated with a slowing of protein bone matrix formation, and an increase in bone resorption.[28] Due to retention of carbon dioxide, or failure to eliminate it, water is retained both intracellularly and extracellularly,[29] increasing the intravascular volume of the blood in which the red cells become larger with the lower pH.[30] Changes in tissue pH associated with the retained CO_2 require compensating modifications in the alkali reserve,[31] other buffer systems, and renal control of body electrolytes. As muscle metabolism is reduced fat and elastic tissue changes are instituted. Respiratory exchange, thoracic pumping, and blood viscosity and coagulability are modified by the degree of physical activity. The effect of reduced effort, carried to the extreme seen in very inactive older persons, contributes to the kitchen midden of tissue degenerations, some of which are reversible, while others are more definitive.

The ultimate result is some form of pathologic change running the gamut of multiple, subtle, or overt changes, even to the extreme of "biochemical death."

Physical limitations may impede those types of activity which can help to retard the development of further increments of abnormality. A patient with crippling rheumatoid arthritis may be forced to a regimen of inactivity because of pain. The reduced activity results in calcium and protein loss. Measures are instituted to maintain blood protein and electrolyte concentrations at normal levels, even if these must be achieved at the cost of somatic sacrifices. New phenomena, such as osteoporosis, appear as complications of the original pathologic state and further impair recovery. The body, subject to the strain of the arthritic process, is also under the stresses of new biochemical accommodations. When a nutritional evaluation of this patient is made, calcium and protein losses, among other changes, are apparent. Can they be said to be the result of an inadequate diet? Would changing the diet change the fasting and tolerance levels? Is it not more likely that the forced reduction in activity has altered the metabolic utilization of those dietary essentials which are available? Are better results due solely to better nutrition or to those sounder procedures which are major influences in the absorption of food? The cause of the nutritional imbalance turns out to be not the elements of the diet but rather the degree of activity. This type of nutritional inadequacy is not to be overcome by dietetic surfeit.

Any evaluation of the nutritional requirements of the older and usually less active body must assess the degree of that body's motions. This is not to infer that vigorous exercise is the answer. A range of activity fitted to individual capacity is preferable to either complete abstinence from all but essential preservative movements, or to obviously excessive efforts.

If enforced rest alone can modify calcium stores in the skeleton, initiate negative protein balance, modify blood pH, promote water retention, change the alkali reserve, reduce the rate of oxidative reactions, slow the pulse, reduce blood pressure, retard the circulatory rate, and lessen muscle tonus *despite* an ideal dietary intake, then activity alone is high on the list of important indices to the nature of nutritional balance.

With reduced activity, the caloric need is usually reduced. The correlation of lessened need with the biochemical effects of lessened activity have a bearing on caloric requirements. Based on activity and aging, the caloric needs are 20 to 30 per kilogram body weight per 24 hours or about 10 to 12 calories per pound.

From these observations, certain conclusions may be drawn:

Given a full diet and proper activity, there will be good utilization and a good physiologic result, with retardation of pathologic processes.

Given a theoretically perfect diet but an inactive patient, the nutritional end-result will probably be unbalanced and unsatisfactory both nutritionally and pathologically.

A poor diet and limited activity will lead to poor utilization, poor results, and an increase of pathologic states.

Proper vital activity may help to convert so-called inadequate diets to better efficiency and retard or reverse abnormal states.

It must be concluded that the degree of activity is a variable of such importance that *the appreciation of physical activity and of recumbency is of importance equal to the appreciation of dietetics.*

Food Intake

The best diet for older age, then, can be established according to these several criteria: the character of physical activity, gastrointestinal structure and function, pathologic disturbances, and chemical balances. New investigations may alter some of these conclusions. For the present, it may be decided that:

(a) Caloric need is dependent on sex, body build, activity, and intrinsic physiologic values, some of which are linked genetically. The range is 20 to 30 calories per kilogram per day. The proportions of fat, protein, and

carbohydrates in the body food pool making up these calories depend on other factors which may have less importance than has been ascribed to them by tradition. Too much emphasis may have been placed on individual food elements; the body may have methods of conversion as yet incompletely understood.

(b) Since the physiologic curve of older age reactivity generally is higher and wider, the food intake should be divided into meals as follows: 2/5, 1/5, and 2/5, or possibly, 4/10, 1/10, 4/10, and 1/10.

(c) With lessened immediate energy needs, a rising metabolic rate paralleling increasing degenerations, and alteration of the glucose tolerance, *carbohydrates* should constitute one-half of the total daily caloric intake. This would average 3 grams, or 12 calories, per kilogram per 24 hours.

(d) With (1) a tendency to loss of protein based on decreased activity, (2) relatively good preservation of protein enzymes, (3) other limitations (hormonal) on positive protein balance, (4) anabolic needs, and (5) evidence that the body handles the end-products of protein metabolism satisfactorily, the *protein* fraction of the diet should constitute at least 20 per cent of the total daily food intake. This would average about 1.35 grams per kilogram per day, or just over 5 calories per kilogram.

(e) With (1) lessening of fuel needs due to reduced activity, (2) reduction in lipase enzymes, (3) abnormal fat deposits in vascular and parenchymal sites, (4) multiple indications of pathologic states related to (abnormal) lipid and steroid metabolism, the *fat* in the diet should be reduced. It might constitute 30 per cent of the daily intake, which would be about 1 gram, or 9 calories, per kilogram per day.

(f) Other dietary adjuncts such as vitamins should be based on specific indication.

Conclusions

Geriatric nutrition has many facets. Extra-nutritional aspects can modify a plan, no matter how skillfully contrived, if proper consideration is not given to each factor. These non-nutritional components of clinical management are inextricably involved with dietary considerations and form an essential part of the treatment of the patient.

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Resumen

Correlaciones clínicas en la nutrición geriátrica

La mejor dieta para la edad avanzada puede ser establecida según varios criterios: el carácter de la actividad física; la estructura y función intestinales; los disturbios patológicos; y los balances químicos.

El requerimiento calórico depiende del sexo, del tipo somático, de la actividad, y de factores fisiológicos intrínsecos, de los cuales algunos están genéticamente encadenados. La gama se extiende de 20 a 30 calorías por kilo/día. Las proporciones de grasas, proteína e hidratos de carbono en el almacén de alimentos del cuerpo que constituyen estas calorías depienden de otros factores que es posible tengan menos importancia de la que se les atribuye por tradición.

Puesto que la curva fisiológica de reactividad en la edad avanzada es generalmente más alta y más amplia, el consumo de alimentos tiene que dividirse en comidas como sigue: 2/5, 1/5, y 2/5—o posiblemente: 4/10, 1/10, 4/10, e 1/10.

Con la disminución de las necesidades energéticas inmediatas, el alza del coeficiente metabólico acompañada por degeneraciones, y con la alteración de la tolerancia a la glucosa, los hidratos de carbono deben constituir la mitad del consumo diario total de calorías: un medio de 3 gms. o 12 calorías por kilo/día.

Con (1) una tendencia a la pérdida de proteína, basada en la actividad disminuida, (2) una conservación relativamente buena de las enzimas proteicas, (3) otras limitaciones (hormonales) del balance proteico positivo, (4) necesidades anabólicas, y (5) evidencia de que el cuerpo utiliza satisfactóriamente los productos últimos del metabolismo proteico, la fracción proteica de la dieta debe constituir por lo menos el 20 por 100 del consumo diario total; un medio de 1,35 gms. por kilo/día, o un poco mas de 5 calorías por kilo/día.

Con (1) disminución del requerimiento calórico debida a la reducida actividad, (2) reducción de las enzimas lipolíticas, (3) depósitos abnormales de grasa en el sistema vascular y parenquimatoso, (4) indicaciones múltiples de estados patológicos relacionados a un metabolismo abnormal de los lípidos y esteroides, las grasas en la dieta deben reducirse. Pudieran constituir un 30 por 100 del consumo diario, lo que sería alrededor de 1 gm. o 9 calorías por kilo/día.

Otros suplementos dietéticos, como las vitaminas, deben basarse en indicaciones específicas.

En la nutrición geriátrica hay que tener en cuenta siempre todos esos componentes extranutritivos que se enredan inextricablemente con las consideraciones puramente dietéticas.

A Comparative Study of "OBESE" CHILDREN *Selected on the Basis of* FAT PADS

By PEGGY CROOKE FRY, B.S.*

IT IS frequently stated that obesity is due either to simple overeating or to glandular disturbances. Many people concerned with this problem once believed that most cases of obesity were the result of glandular dysfunction, and based their work on this principle. The results have been disappointing, for the problem of obesity has not been completely solved by the administration of hormonal substances. Presently, the pendulum of opinion has swung toward the hypothesis that simple overeating is the basic cause of obesity in approximately 95 per cent of cases. Most authorities would agree with Barborka's statement, "It is indeed true that fat comes only from food and those who wish to get rid of accumulated body fat must eat less than is required to meet the energy requirements of the body."[1]

The present investigation was made primarily in an attempt to discover some developmental characteristics of obese children as compared to "normal" children and, secondarily, to test the truth of Barborka's and similar hypotheses.

MATERIALS AND METHODS

The materials used in this investigation were selected from data gathered on children who participated in the Forsyth Child Growth Program. The group of children included in the present investigation was selected on the basis of the presence of *fat pads* or folds, as seen in somatotype pictures (Figs. 1, 2, 3), rather than on the basis of excess weight above a given standard for their age, height, and sex. They were looked upon as a single group, thus avoiding the complexities of a classification such as the 5-fold one used by Reynolds and Asakawa[2] of obese, relative obese, mixed obese, relative mixed obese, and not obese. From here on, the sample will be referred to as the fat-pad group.

In order to be included in the sample, it was necessary for each child to exhibit pads or folds of fat in at least two of three regions—dorsal, abdominal, or trochanteric.

The absence of an adequate working definition of obesity in medical terminology was an important reason for using the criterion mentioned above in the selection of the group of obese children studied. For example, one reference work, the *American Illustrated Medical Dictionary,* has defined obesity rather vaguely as "an excessive accumulation of fat in the body; corpulence; fatness."[3]

When the study was begun, a series of 414 children (187 boys and 227 girls), ranging in age from 4 through 14, was included in the Forsyth Child Growth Program. All these individuals were referred to the Nutrition Department for one or more of the following reasons: (a) they were patients in the Orthodontic Department and thus routinely referred to the Clinic; (b) they displayed striking dental abnormalities; (c) they had noticeably poor hygiene or nutrition.

The fat-pad study was carried out on a subgroup of 39 of the above-mentioned 414

From the Forsyth Dental Infirmary for Children, Boston, Massachusetts.

A portion of this paper was read at the 21st Annual Meeting of the American Association of Physical Anthropologists, New York, N. Y., March 1952 (*Amer. J. Phys. Anthrop.*, 1952, n. s. 10, 262–263).

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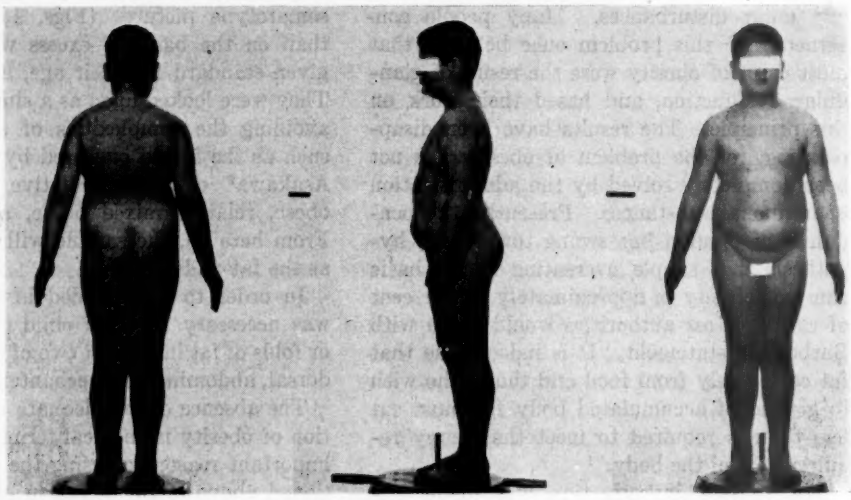
Figure 1



Somatotype pictures of typical "fat-pad" children

Figure 2

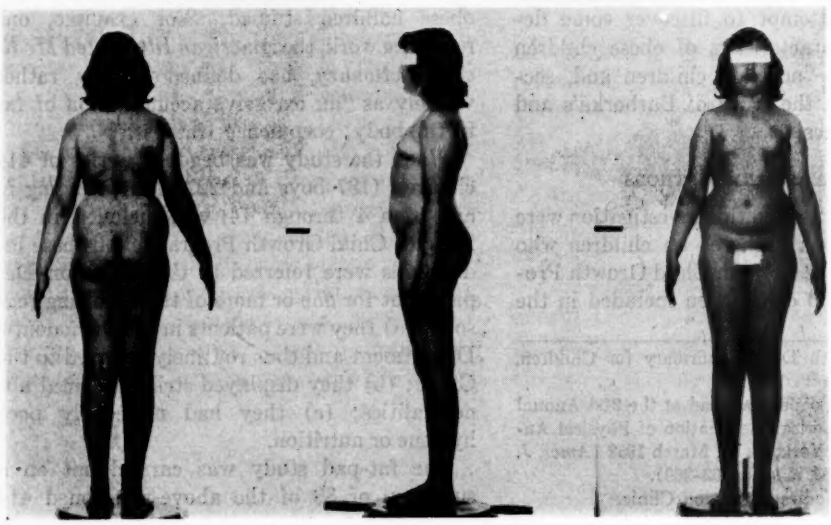


Figure 3

children which consisted of 13 boys and 26 girls, ranging in age from 5 through 14 years.

For purposes of comparison, a control group of 50 children was selected at random. The sex ratio of this group was 24 boys to 26 girls, ranging in age from 4 through 13 years.

The same study material was obtained on each child in the two groups, with the exception of tooth emergence information, which was not gathered for members of the control group. The majority of measurements on a single child were taken within a six-month period. The following is a description of the determinations made in this study and the methods by which they were obtained.

1. Standard scores of height and weight were calculated from Forsyth-Fels[4] tables and plotted in relation to each other. The height and weight data for each of the 89 children were also plotted on a Wetzel Grid.

2. The level of development of each child was measured in terms of tooth emergence, skeletal maturation, and sexual maturation. Standard scores were determined from the eruption data on the permanent teeth of all the children in the fat-pad group. These standard scores were calculated by a dentist after a thorough appraisal of each child's dental record and successive sets of dental casts, utilizing the eruption standards set up by Hurme.[5] The bone age of each child was determined by means of wrist x-rays for 76 of the children in the two groups, using the criteria of Todd[6] and Greulich and Pyle.[7] From these data, furnished by two physical anthropologists, a bone age quotient (B.A.Q.) was calculated.

$$\frac{\text{Bone Age}}{\text{Chronological Age}} \times 100 = \text{B.A.Q.}$$

Sexual maturity was estimated from the somatotype photographs of every child in the two groups who gave any indication of adolescence. The ratings were made by three physical anthropologists and were based on the estimation of stage of areolar development, breast size or shape, amount of pubic hair and, in a few instances, degree of development of the genitalia in boys. The standards used in these ratings were those of Crawford,[8] Shuttleworth,[9] and Garn.[4] It is believed that these criteria are more critical than those used by Bruch.[10]

3. Data were obtained on the systolic and diastolic blood pressures of 37 of the fat-pad group and on all 50 of the control group. All of these children had made at least two visits to the clinic, and several of them had attended the clinic as much as ten times. These routine determinations were made according to the recommendations of the American Heart Association, Inc., and the figures obtained during the most recent visit of a child were used in this study.

4. The postnatal developmental histories of the children were studied in an effort to determine the age of teething, walking, and talking. The histories that were investigated were given by the mothers to nutritionists during interviews at the clinic. There were varying degrees of accuracy in the reporting of these ages by the mothers.

5. An important phase of this investigation was the obtaining of a record of the protein and caloric intake of these children. The time period for the dietary study ranged from 3 to 8 days. During interviews, mothers were given "What I Eat" booklets and definite instructions on keeping daily records, except in the case of adolescent children, who were asked to keep their own dietary records. Mothers and adolescents were requested to report food intakes in terms of common household measures, rather than use of unreliable terms such as "a small portion, a tiny bit, etc." in describing quantities of food eaten. They were urged not to alter the usual family fare for the period covered by the record. On the basis of the dietary information thus obtained, the caloric and protein intake for a 24-hour period was calculated for each child. Each child's average intake per 24-hour period was compared with the quantities recommended by the National Research Council for his age.[11] In making its recommendations, the National Research Council suggests that 10.5 to 13.3 per cent of the total calories per day be derived from protein foods.

6. The family background and history of all 89 children were studied. This information, gathered by personal interview and by observations, was analyzed with respect to four considerations: (a) the birth order of siblings within each family; (b) the degree of obesity or stockiness of the mother; (c) the ethnic origin of the children; and (d) the psychologically important characteristics of the home environment. After an analysis of the home environment, the children were divided into two groups: (1) emotionally unstable children: those who seemed to have a disorganized home environment due to such causes as divorced or separated parents, emotional instability in members of the family group, undue economic strain in the family, or severe or prolonged illness of one parent; (2) emotionally stable children: those whose environments seeemed relatively free of disturbing factors. In addition, observations of the mothers were made by the nutritionists during interviews and were studied to determine the importance of obesity as a possible inherited characteristic. The ethnic origin and the birth order of the children were obtained by interview with one of the parents. The classification used in the analysis of the birth order is that of Wile and Davis.[12]

7. The weight gain of the mother during pregnancy and the birth weight of the infants, as given by the mothers, were investigated. For statistical purposes,

TABLE I Group Data on Fat-Pad and Control Girls

	Number	Range	Mean	Standard error of the mean	Standard deviation
Fat-Pad Group—Girls:					
Systolic blood pressure (mm. Hg)	24	84 – 150	118.46	±2.82	±13.80
Diastolic blood pressure (mm. Hg)	24	56 – 100	72.67	±2.05	±10.04
Standard score on height (cm.)	26	− 1.73 − + 2.12	0.02	±0.20	± 1.00
Standard score on weight (lb.)	26	− .45− + 3.65	1.43	±0.25	± 1.26
Standard score on tooth eruption	26	− .56− + 1.59	0.39	±0.12	± 0.60
Wrist ossification quotient	22	68.48− 152.63	105.45	±3.70	±17.37
Mother's weight gain in pregnancy (lb.)	18	5.0 – 75.0	24.94	±4.25	±18.05
Weight at birth (lb.)	24	5.0 – 10.0	6.63	±0.27	± 1.30
Age of teething (mo.)	21	4.0 – 18.0	8.17	±0.65	± 2.97
Age of talking (mo.)	19	12.0 – 36.0	17.97	±1.37	± 5.96
Age of walking (mo.)	21	8.0 – 18.0	13.21	±0.62	± 2.84
Mean age (yrs.)	26		$9^{5}/_{12}$		
Control Group—Girls:					
Systolic blood pressure (mm. Hg)	26	94 – 144	113.92	±2.30	±11.70
Diastolic blood pressure (mm. Hg)	26	46 – 80	69.00	±1.33	± 6.80
Standard score on height (cm.)	26	− 2.57− + 1.17	−0.60	±0.21	± 1.06
Standard score on weight (lb.)	26	− 1.86− + 1.69	−0.50	±0.19	± 0.95
Wrist ossification quotient	22	66.54− 121.66	92.49	±2.94	±13.80
Mother's weight gain in pregnancy (lb.)	17	12.0 – 60.0	20.79	±2.61	±10.77
Weight at birth (lb.)	22	5.0 – 10.0	7.09	±0.31	± 1.45
Age of teething (mo.)	19	4.0 – 13.5	7.92	±0.64	± 2.78
Age of talking (mo.)	22	10.0 – 21.0	18.02	±1.41	± 6.60
Age of walking (mo.)	22	7.0 – 16.0	13.11	±0.44	± 2.07
Mean age (yrs.)	26		$9^{1}/_{12}$		

TABLE II Group Data on Fat-Pad and Control Boys

	Number	Range	Mean	Standard error of the mean	Standard deviation
Fat-Pad Group—Boys:					
Systolic blood pressure (mm. Hg)	13	100 – 140	115.69	±3.21	±11.57
Diastolic blood pressure (mm. Hg)	13	62 – 100	80.62	±2.85	±10.26
Standard score on height (cm.)	13	− 0.88− + 2.07	0.90	±0.23	± 0.83
Standard score on weight (lb.)	13	1.14− 5.63	2.86	±0.39	± 1.39
Standard score on tooth eruption	13	− 0.89− + 1.13	0.27	±0.18	± 0.64
Wrist ossification quotient	9	73.47− 133.64	108.09	±5.57	±16.72
Mother's weight gain in pregnancy (lb.)	6	12.5 – 40.0	26.67	±3.80	± 9.30
Weight at birth (lb.)	11	5.0 – 10.0	7.27	±0.39	± 1.30
Age of teething (mo.)	11	6.0 – 13.5	9.14	±0.75	± 2.47
Age of talking (mo.)	9	9.0 – 24.0	20.11	±1.48	± 4.44
Age of walking (mo.)	11	10.0 – 18.0	12.86	±0.80	± 2.65
Mean age (yrs.)	13		$10^{6}/_{12}$		
Control Group—Boys:					
Systolic blood pressure (mm. Hg)	24	96 – 138	113.67	±2.12	±10.38
Diastolic blood pressure (mm. Hg)	24	56 – 86	67.67	±1.85	± 9.08
Standard score on height (cm.)	24	− 2.67− + 1.84	−0.49	±0.26	± 1.26
Standard score on weight (lb.)	24	− 2.39− + 1.25	−0.47	±0.16	± 0.80
Wrist ossification quotient	23	65.00− 116.48	92.83	±2.88	±13.80
Mother's weight gain in pregnancy (lb.)	17	6.0 – 45.0	23.71	±2.56	±10.57
Weight at birth (lb.)	21	4.0 – 10.0	7.14	±0.31	± 1.44
Age of teething (mo.)	19	3.0 – 12.5	7.03	±0.51	± 2.20
Age of talking (mo.)	19	12.0 – 27.0	21.08	±1.99	± 8.68
Age of walking (mo.)	20	9.0 – 18.0	13.20	±0.49	± 2.20
Mean age (yrs.)	24		$9^{8}/_{12}$		

all measurements were rounded off to the nearest pound, except if an approximation in terms of two figures was given, e.g., a 15- to 20-pound gain during pregnancy was recorded as an increase of 17 pounds and 8 ounces.

8. A medical evaluation of each patient and his consistency in maintaining the same percentile rating of weight was studied by the use of height-weight charts made by H. C. Stuart.[13] Each child was given a complete medical examination and a somatotype photograph was taken at each visit to the clinic. All children were considered essentially healthy if they were not suffering from any detectable diseases or deficiencies. This medical evaluation was made by the staff pediatrician on each member of the fat-pad group. In evaluating the latter as either obese or not obese clinically, the following considerations were borne in mind: (a) the adequacy with which the child could physically compete with his playmates; (b) the weight chart of the patient for the length of time that he attended the clinic; (c) habits of eating; (d) general appearance; (e) age; (f) personality.

The height and weight of a child were plotted against his or her age at the time of each visit on Stuart's charts for observing the growth of children. These charts give the child a percentile rank at each age. Since many of the children had been seen as often as ten times, at six-month intervals, their progress in height and weight was known for a considerable span of time.

9. The health histories of the children were studied from birth until the time of writing this article (1952). In organizing this information for analysis, the classification used by Bayer and Snyder[14] was followed. Muscular and refractory lesions of the eyes, deviations in weight, alignment of the teeth, or carious lesions were omitted from the classifications.

10. Very rough psychological evaluations were formulated for each child in terms of: (a) degree of play activity; (b) gregariousness or introversion; and (c) presence or absence of pernicious or noxious habits. Under the term noxious habits the following were included: nail biting, pulling off of toe nails; sucking of thumb, finger, or lip; twitching; "tic" of the eye; pushing tongue against teeth; "nervous" coughing; twiddling of thumbs; stuttering; day-dreaming; rolling, chewing and spitting pieces of pencils; and scratching. These activities must have been performed frequently enough by the child to be very noticeable, and even annoying, to the observers. The observations made by several independent observers, dental interns, pediatrician, nutritionists, and parents were studied in order to see if there were any marked differences between the fat-pad and control groups in these respects.

Results

The number of children studied, the ranges, the means and their standard errors, and the standard deviations of all the measurements listed previously on which these statistics could be calculated are given in Tables I and II. The standard error of the difference between the means for (a) fat-pad girls and fat-pad boys, (b) fat-pad girls and control girls, and (c) fat-pad boys and control boys were calculated. Following this, the "t" test was applied to these measurements, and all those which yielded statistically significant results are shown in Table III.

TABLE III

Tests of Significance

	"t" test	Level of significance
Fat-pad girls vs. fat-pad boys—diastolic blood pressure	2.22	.05
Fat-pad girls vs. fat-pad boys—standard score on height	2.67	Greater than .01
Fat-pad girls vs. fat-pad boys—standard score on weight	3.14	Greater than .01
Fat-pad girls vs. control girls—standard score on height	2.14	.05
Fat-pad girls vs. control girls—standard score on weight	6.12	Greater than .01
Fat-pad girls vs. control girls—wrist ossification quotient	2.68	Greater than .01
Fat-pad boys vs. control boys—diastolic blood pressure	3.85	Greater than .01
Fat-pad boys vs. control boys—standard score on height	3.48	Greater than .01
Fat-pad boys vs. control boys—standard score on weight	9.00	Greater than .01
Fat-pad boys vs. control boys—wrist ossification quotient	2.56	.02
Fat-pad boys vs. control boys—aging of teething	2.34	.05

The sample of 39 children represents 9.4 per cent of the total of 414 children participating in the Forsyth Child Growth Program. To determine the significance of the sex ratio of 13 boys to 26 girls as compared to the sex ratio of the total series of 187 boys to 227 girls,

chi-square was computed and found to be not statistically significant. Chi-square was also computed to test the representativeness of the fat-pad group and the growth program group as a reflection of the United States boy-girl ratio, and found to be significant at the 5 per cent level.

From these figures, it can be seen that the fat-pad group and the growth program group represent a true random sample, for they accurately reflect the ratio between boys and girls in the United States. On the basis of the information presented on the ratio of boys to girls in the fat-pad group, it can be seen that the sample presented here follows the general tendency of more girls than boys being overweight in a given population.

In the fat-pad group, 24 girls out of 26 were above average in *weight,* and only 2 were below average. All 13 boys in the fat-pad group weighed over average. Twelve of the girls in the fat-pad group were above the mean in *height* and 14 were below the mean in height. All but 2 of the 13 boys were above the mean in height. The results among the control group children were: 20 girls with minus standard scores and 6 girls with plus standard scores with respect to weight; 17 boys with minus standard scores and 7 boys with plus standard scores in weight; 9 girls on the positive side and 17 girls on the negative side in height; and 10 boys above and 14 boys below the mean in height. The differences between these measurements, as evaluated by use of the "t" test, indicate that the fat-pad group differs significantly from the control group with respect to height and weight.

Six of the 26 girls in the fat-pad group were retarded in *tooth eruption,* while one was on the mean, and 19 were advanced in this respect. Three of the 13 boys were retarded in tooth eruption, with one boy on the mean and nine advanced. The "t" test showed that there was no statistically significant difference between the sexes.

Fourteen of 22 fat-pad girls and 6 of 9 fat-pad boys had *bone age* quotients above 100. In the control group, there were 6 of 22 girls and 8 of 23 boys who had bone age quotients above 100. The difference between the quotients of the fat-pad boys and girls was not statistically significant, but the differences between fat-pad boys and control boys and fat-pad girls and control girls were significant; i.e., 64.5 per cent of the fat-pad children were advanced for their age in skeletal maturation, whereas this was true of only 31.0 per cent of the control group children.

Forty-six of the 89 children in the two groups were in the prepuberty period. The 43 remaining children were rated on *sexual maturation,* the findings being shown in Table IV. A chi-square test indicated no significant difference between any groups. The fat-pad children were neither more advanced nor more retarded than the control children in sexual maturation. Bruch reported that "Early puberal development is the rule for obese girls and is not uncommon for obese boys,"[15] and according to Schonfeld, ". . . obese boys usually mature earlier than do boys with normal weight."[16] The fat-pad children as a group were not distinctly advanced in puberal development, and in this sense, are not comparable to the obese children studied by Bruch and Schonfeld. However, it is seen by comparison with the control group of children that they were not delayed in sexual maturation.

TABLE IV

Sexual Maturation

	Fat-pad group		Control group	
	Girls	Boys	Girls	Boys
Prepuberty	10	6	15	15
Normal	4	2	6	3
Advanced	7	4	1	1
Very advanced	2	0	0	5
Retarded	3	1	2	0
Very retarded	0	0	2	0
	26	13	26	24

Upon analysis of the systolic and diastolic *blood pressure* data, it was evident that there was no statistically significant difference between the systolic blood pressure of either sex in either group or between the diastolic blood pressures of the fat-pad girls and control girls. There was, however, a significant difference between the diastolic blood pressure of the fat-pad girls and boys, and between the fat-pad boys and the control boys.

As was stated previously, there were varying degrees of accuracy in the reporting of the *age of teething, walking, and talking.* It was found that mothers tended to have a better idea of any particularly early or late stages of their children's growth. For each child studied there were from 7 to 12 mothers who either had no idea, or only a very vague recollection of the age when their child reached a particular point in development. Vaguely estimated ages of development were not used in arriving at the statistics presented in Tables I and II. Statistical evaluation of the data showed that there was no statistically significant difference between the sexes in either group in any of these three developmental aspects, except in the case of the age of teething in the fat-pad boys as compared to the control boys.

Dietary information was obtained on 36 of the 39 children in the fat-pad group and on 44 of the 50 children in the control group. The data on protein and caloric intake of these 80 children are summarized in Tables V, VI, VII, and VIII.

TABLE V

Protein Intake of Girls

Age	Fat-pad group		Control group	
	Number	Range of *N.R.C. recommendations	Number	Range of *N.R.C. recommendations
		%		%
1– 3	0	—	2	14 to 21
4– 6	2	15 to 16	6	11 to 25
7– 9	9	7 to 18	5	10 to 23
10–12	13	11 to 20	11	7 to 19
13–15	0	—	3	15 to 17

* N.R.C. = National Research Council.

TABLE VI

Protein Intake of Boys

Age	Fat-pad group		Control group	
	Number	Range of *N.R.C. recommendations	Number	Range of *N.R.C. recommendations
		%		%
1– 3	0	—	1	16
4– 6	0	—	2	15 to 17
7– 9	3	12 to 14	5	13 to 22
10–12	6	12 to 18	8	11 to 21
13–15	3	13 to 15	1	11

* N.R.C. = National Research Council.

TABLE VII

Caloric Intake of Girls

Age	Fat-pad group		Control group	
	Number	Range of *N.R.C. recommendations	Number	Range of *N.R.C. recommendations
		%		%
1– 3	0	—	2	104 to 131
4– 6	2	86 to 134	6	93 to 147
7– 9	9	73 to 231	5	69 to 120
10–12	13	64 to 101	11	60 to 115
13–15	0	—	3	98 to 116

* N.R.C. = National Research Council.

TABLE VIII

Caloric Intake of Boys

Age	Fat-pad group		Control group	
	Number	Range of *N.R.C. recommendations	Number	Range of *N.R.C. recommendations
		%		%
1– 3	0	—	1	95
4– 6	0	—	2	89 to 117
7– 9	3	118 to 130	5	88 to 154
10–12	6	56 to 143	8	71 to 136
13–15	3	56 to 88	1	62

* N.R.C. = National Research Council.

Among the fat-pad children, the per cent of total calories consumed differed from the National Research Council recommendations by from 64 to 231 per cent for the girls and from 56 to 143 per cent for the boys. The variation in the percentage of total calories from protein foods was from 7 to 20 per cent for the girls and 12 to 18 per cent for the boys. There were 26 (72.2 per cent) of the entire fat-pad group who fell below the caloric recommendations for their age group, while 28 (77.8 per cent) of them were above the recommendations for protein intake.

The per cent of total calories consumed, as recommended by the National Research Council, ranged in the control group from 60 to 147 per cent for the girls and from 62 to 154 per cent for the boys. The variation in the percentage of total calories from protein foods was 7 to 25 per cent for the girls and 11 to 22 per cent for the boys. There were 21 (48 per cent) of the control group who fell below the caloric recommendations for their age group, whereas 30 (68 per cent) of them were above the recommendations for protein intake.

TABLE IX
Comparisons of Family Disorganization

	Stable	Disorganized
Boys:		
Fat-Pad	9	4
Control	19	7
	28	11
Girls:		
Fat-Pad	18	8
Control	18	6
	36	14

When the *family histories* of all 89 children were analyzed as to the stability or disorganization of their family environment, the results shown in Table IX were obtained. A chi-square test indicated that there was no statistically significant difference between the fat-pad and control groups— i.e., both groups were made up of comparable proportions of stable and disorganized homes.

Bruch[17] feels that the significance of food and its consequent intake are connected with the emotionality of the child. The findings of the present author do not support those reported by Bruch, because the majority of the fat-pad group were classified as emotionally stable children. We may infer that the presence of fat pads in this group is not due to a neurosis expressed by overeating.

In any consideration of obesity, the question arises as to why the condition came into being. Schlutz[18] feels that two of the primary factors involved are (a) familial tendencies, and (b) racial factors.

Observations that the nutritionists made during interviews with the mothers of fat-pad and control group children were studied to determine the importance of obesity or stockiness as a *parental factor*. Estimates based on the height of the mother as compared to weight were recorded for 35 of the 39 in the fat-pad group. Fourteen (40 per cent) of the mothers were classified as stocky or overweight, 8 (22.8 per cent) of the mothers were of medium build, and 13 (37.2 per cent) of the mothers were considered to be thin or of light build. Estimates on 44 of the mothers of the control group children were 11 (25 per cent) stocky, 16 (36.4 per cent) medium build, and 17 (38.6 per cent) thin or of light build. When the chi-square was computed, the results did not prove to be statistically significant for either sex; therefore, the findings in this investigation were not in accord with the hypotheses of Schlutz,[18] Reynolds,[19] and Woods.[20] The mothers of the fat-pad children are not themselves fat, even though the dietary habits of the entire family are likely to be similar. There does not seem to be a maternal hereditary factor involved, as Bronstein[21] has reported.

An analysis of the *ethnic origin* of the sample showed that of the 39 fat-pad children, 27 were of Northwest European ancestry, and 12 of South European descent. Thirty-four of the control group were of Northwest European ancestry, 2 of Central European descent, and 14 of South European ancestry. The South European group includes children of Jewish origin. All of the children were American-born. A chi-square test of ethnic origin and degree of obesity, as measured by standard scores on weight, did not prove any statistically significant association between these variables for either sex.

Bruch found in her study that ". . . the most severe forms were met with in children of South European stock. . . ."[10] In the present study, although extreme cases of obesity who are of South European ancestry can be selected, extreme cases who are of Northwest European ancestry can also be found. In short, Bruch's findings are not borne out by the data.

In some instances during the investigation of *birth order* among the control and fat-pad children, a child could be placed in several categories. When this occurred, a decision was made as to which category was the most outstanding and also which best described the parental appraisal of the child; for instance, patient no. 78 was a second child and was 12 years younger than her brother. She was placed in the group "Separated by Great Age Difference" because this phrase was a more accurate reflection of her parents' attitude.

Each child was counted only once. The criteria for selection of seven years as an ade-

quate "Separated by Great Age Difference" were: (a) the previous child is in school by 7 years of age, so the era of his being at home with the mother all day is past; (b) the loss of position by the previous child as "baby" of the family is accentuated by this time. The birth order of the 89 children is given in Table X. The fat-pad group averaged two to three children per family, while the control group averaged three to four children per family.

TABLE X

Birth Order in Relation to Other Siblings

Class		Fat-pad group Girls (N = 26)	Fat-pad group Boys (N = 13)	Control group Girls (N = 26)	Control group Boys (N = 24)
		%	%	%	%
I	First born	38.5	38.4	30.8	50.0
II	Second born, not youngest	7.7	23.1	19.2	12.5
III	Other positions (not first, second or youngest)	—	—	11.5	4.2
IV	Only child (first or not first born)	19.2	7.7	3.8	—
V	Youngest in the family	30.8	23.1	27.0	29.1
VI	Separated by great age difference (seven years or more)	3.8	7.7	7.7	4.2

In the fat-pad group, information on the *mother's weight gain* during pregnancy and the infant's birth weight was obtained from 24 of the mothers and for 35 of the children. In the control group, the data were available for 34 mothers and 43 children. One mother in each group reported a loss in weight, the extent of which could not be determined, and therefore this information was not used in arriving at the statistics presented in Tables I and II.

The differences between the children and the differences between the mothers did not prove to be statistically significant when analyzed by sex and by the group to which they belonged. Not one of the 4 groups of mothers differed markedly in its mean weight gain. And not one of the 4 groups of children differed markedly in its mean birth weight. Bruch reported that ". . . a normal or even low [birth] weight is frequently encountered in children who grew fat at an early age."[10] The findings of the present investigator clearly bear out her point, for a high birth weight, which is frequently considered a predisposition to obesity, was found only infrequently.

The medical evaluation of the fat-pad group showed that there were 20 clinically obese children (12 girls and 8 boys), and 19 non-obese children (14 girls and 5 boys). An examination of the Stuart height-weight chart for each child showed that 59 per cent (17 girls and 6 boys) in the fat-pad group and 24 per cent (4 girls and 8 boys) in the control group consistently increased in their percentile ratings of weight during the time they were observed. 2.6 per cent (1 boy) of the fat-pad group and 4 per cent (1 boy and 1 girl) of the control group decreased in their percentile ratings of weight. 38.4 per cent (9 girls and 6 boys) of the fat-pad group and 72 per cent (21 girls and 15 boys) of the control group remained in the same percentile rank for their weight.

The types and incidence of illness among the children in both groups are listed in Table XI. Not included in this list are 32 other acute and chronic illnesses, of major and minor importance. In these, too, no significant differences between the two groups were apparent.

The gross appraisals of personality, play activities, and personal habits of the fat-pad and control children by means of observations made by independent observers yielded the figures presented in Table XII.

Discussion and Conclusions

On a group basis, there was no significant difference between children with fat pads and

TABLE XI

Illness Experience of Fat-Pad and Control Children

	Fat-pad		Control	
	Boys (N = 13)	Girls (N = 26)	Boys (N = 24)	Girls (N = 26)
Communicable diseases				
Rubeola	10	21	20	18
Varicella	8	15	16	17
Pertussis	4	10	5	8
Parotiditis	6	2	11	7
Rubella	1	3	0	0
Scarlatina	3	2	5	3
Colds				
1 to 2 per year	3	12	10	11
3 to 4 per year	4	4	3	3
5 to 8 per year	2	4	5	4
Upper respiratory infections other than colds	5	9	11	6
Allergies				
Hives	0	0	0	1
Hay fever	0	1	1	0
Asthma	3	0	2	1
Gastro-intestinal and abdominal disturbances	3	7	2	6
Accidents				
Eye injury	1	1	0	0
Bone fractures	2	4	3	2
Dislocations and sprains	1	1	1	0
Broken teeth	0	1	1	1
Cuts, with stitches	0	0	3	2
Shock	0	0	1	0
Concussion with motor disturbance	0	0	2	0
Surgery				
Circumcision	0	0	4	0
Tonsillectomy and/or adenoidectomy	10	10	13	12
Myringotomy	1	1	1	1
Appendectomy	0	1	1	0
Excision of benign skin lesion	0	0	1	1
Double mastoidectomy	0	0	0	1

children without fat pads with respect to:

(a) the rate at which they approached puberty;

(b) the incidence of disorganization in the home, causing overt emotional disturbances in the child;

(c) the influence of maternal heredity on body build;

(d) the influence of ethnic origin on tendency toward obesity;

TABLE XII

Gross Psychological Evaluation

	Fat-pad group		Control group	
	Girls (N = 26)	Boys (N = 13)	Girls (N = 26)	Boys (N = 24)
	%	%	%	%
Play activities:				
Active	50.0	30.8	65.4	83.3
Moderately active	42.4	30.8	23.1	4.2
Inactive	3.8	23.1	—	4.2
No data	3.8	15.3	11.5	8.3
Personality:				
Friendly	53.9	61.5	61.6	83.3
Less friendly	34.6	23.1	26.9	4.2
Unfriendly	3.8	7.7	—	—
No data	7.7	7.7	11.5	12.5
Noxious habits:				
Presence	53.9	38.4	46.1	50.0
Absence	19.2	7.7	30.8	37.5
No data	26.9	53.9	23.1	12.5

(e) the weight gain of the mother during pregnancy and the birth weight of the infant.

As a group, the 39 fat-pad children tended to be above the mean in stature and weight. It is interesting to note that while 16 (41 per cent) of the group were below the age norm in stature, only 2 (5 per cent) were below the age norm in weight. This indicates that while a good proportion of the fat-pad group is shorter than normal and heavier than normal, the majority is taller and heavier than normal.

A definite majority (72 per cent) of the fat-pad group was advanced in the eruption of its permanent dentition. Although little is known of the relationship between tooth emergence and the tendency toward fat pads, the evidence found here seems to indicate a positive correlation. Talmers[22] showed that a positive correlation existed between advanced stature and advanced tooth eruption and her findings are also confirmed by the present study. Bronstein[23] found that tooth eruption was accelerated among the 46 obese children he studied who had no symptoms of Fröhlich's syndrome or any glandular dysfunction.

Since two-thirds of the fat-pad group had bone age quotients above 100, it can be seen that a definite majority of the sample was advanced in skeletal maturation. The findings here are in accord with those reported by most authors who have investigated this aspect of the problem (Bruch,[10,15,24] and Reynolds[19]).

The question of the relationship between obesity and overnutrition should be raised here, for the accelerated development of the fat-pad children in stature, weight, tooth emergence, and skeletal ossification could be explained at least partially in this manner. Very few studies have been made on the effects of persistent overnutrition, and a search of the literature has failed to uncover any such studies in humans. Most of the work has dealt with the results of undernutrition, of which the deprivations imposed by war are a prime example. Long-continued childhood malnutrition has resulted in marked delay in statural and puberal development, as well as in weight deficiency for chronological age. It does not seem unreasonable that prolonged overnutrition would have reverse effects.

The one contradiction of the application to the fat-pad children of the hypothesis proposed above is that the fat-pad and control children do not differ significantly from one another in terms of sexual maturation. On the basis of the overnutrition hypothesis, it could be anticipated that puberty would take a more rapid course in the fat-pad group, but such is not the case, since the two groups approached puberty at the same rate.

The present study offers no evidence to substantiate theories that attempt to explain obesity on the basis of hypothyroidism and/or hypopituitarism. It has been firmly established that hypofunctioning of either of these glands results in delayed puberal development and growth retardation. The fat-pad children studied needed no endocrine therapy to promote growth because they showed general acceleration rather than retardation of the processes of growth and maturation.

It is believed that the explanation of the significant differences in diastolic blood pressure of the fat-pad girls and boys, and the fat-pad boys and control boys is two-fold in nature: (a) the onset of adolescence causes an increase in blood pressure in both males and females; (b) excessive deposits of subcutaneous fat interfere with the mechanics of obtaining an accurate blood pressure reading. Both of these factors are felt to be operative in the investigation. The personal equation can be ruled out as a factor in the reporting of blood pressure data, since all of the measurements were made by the author.

Stuart[25] has reviewed the changes in blood pressure which occur in males and females during the adolescent period. In this study, the fat-pad boys presented more extremes in obesity than did the fat-pad girls. There were 5 (38.5 per cent) of the fat-pad boys with standard scores for weight above 3.00, whereas only 4 (15.4 per cent) of the fat-pad girls had such high scores.

The findings partially refute the belief that most obesity is due to endocrine dysfunction of the hypothyroidism type. Some well-known characteristics of hypothyroidism are delay in dentition and in mental and locomotor development, but the fat-pad children were not different from the control children as a whole in ages of teething, walking, and talking. In the age of teething, the fat-pad boys were behind the control boys. The data on these aspects show that "normal" development was the rule, not the exception, among the children in both groups. This can be further verified by comparison of the author's figures with those of Gesell,[26] and Watson and Lowrey.[27] The slight differences between the developmental ages given by these authors and those found in the present study are probably due to inaccurate observation, misinterpretation, and poor memory on the part of the mother.

An unexpected finding is that the fat-pad boys, although retarded in age of teething, are significantly advanced in skeletal maturation. It is generally believed that bone ossification and eruption of dentition go hand-in-hand, as is evidenced by comparing the fat-pad and control girls; if the hypothyroidism theory is correct, the fat-pad girls should be retarded in age of teething, which they are not. An explanation of the discrepancy within the group of fat-pad boys is lacking at the present time.

The dietary study was limited to two food constituents—proteins and calories, for the following reasons: (a) calories are indicative of the energy intake per day; (b) proteins are the most important single nutrient in the diet, they have the highest specific dynamic action

of all the food items, they are needed for building and maintaining body tissues. Knowing the caloric yield of the daily protein consumption, it is relatively easy to calculate the proportion of the diet composed of fats and carbohydrates—the energy-yielding and adipose tissue-building nutrients. Fats and carbohydrates furnished from 80 to 93 per cent of the total calories per day for the children in the fat-pad group, while 75 to 93 per cent of the total daily calories of the control group were furnished by fats and carbohydrates.

Generally speaking, the protein intake per day was more than adequate in both groups of children. Three-quarters of the children in each group exceeded National Research Council recommendations in this respect. The *average* caloric intake of the fat-pad children was quite close to the recommendations, yet the range of variation was wide, and the vast majority (almost three-fourths of the sample) had a caloric intake below these recommendations. Only 48 per cent of the control group had a caloric intake below National Research Council recommendations. It cannot be said, on the basis of the analysis of dietary intake, that these children have fat pads solely because they overeat. Rather, these findings are in direct opposition to those who feel that obesity is the result of overeating. The Forsyth fat-pad group as a whole did *not* overeat.

The majority of the children in the two groups are long-term participants in the Forsyth Child Growth Program, and on numerous occasions have recorded their weekly food intake for clinical appraisal. It was seen from the dietary records that these patients and their families had not changed their dietary patterns for only one week or for the purpose of misleading the clinic personnel. Had this been done, consistency would not have been evident in the records of each child from year to year. The reliability of the dietary information is enhanced by these facts.

The familial status of the fat-pad children in relation to their siblings and the average size of the families of the two groups revealed some figures which were contradictory to those reported by Bruch[17] and Bronstein.[21] The children with fat pads came from smaller families than did children who had no fat pads. Of the fat-pad children, 46 per cent were in the position of "baby" of the family for a period of at least 7 years, (i.e., Classes IV, only child; V, youngest; VI, separated by great age difference). In the control group, 36 per cent of the children were considered "baby" of the family for at least the first 7 years of life. Bruch[17] reported that 70 per cent of the obese children she studied were the "only," or the youngest children in their families, and that the average family size was less than two siblings in each family.

Despite the fact that obesity is one of the most common anomalies found in the general population today, it lacks a precise medical definition. Many studies have been made of obesity in children and in adults, but we still have no clear understanding of the causes or effects of obesity or overweight in any age group. In the present investigation, the medical evaluation of the fat-pad group was hampered by our inadequate knowledge of what to look for. About all we know is that the physiological requirements of growth and development are far different from those for mere increase in weight of an adult.

It is the exception rather than the rule to see a child in a clinic who remains in the same percentile for height and weight over a period of several years. If longitudinal studies of sufficient magnitude, rather than cross-sectional studies, were the basis for height-weight charts, it could be more accurately determined, perhaps, whether or not a child is "normal" for his age. Reynolds[19] and Simmons[28] have reported generally high weight-for-age correlations among the children included in their longitudinal studies.

For the reasons discussed above, no explanation of the medical findings or evaluation of the percentile ratings of weight is presented in this report. The data are included with the hope that they may be used for comparative purposes in future investigations, when the phenomena of obesity and growth and development of children are better understood.

In tabulating the illness experience of the 89 children, a rating to indicate the severity of each illness could not be given, as the data

were not sufficiently accurate. In most instances, the mother related the illness to a member of the clinical staff, but the child was not seen at the time of the illness. Clinical examinations were made primarily for routine observational purposes and thus the case lacked laboratory reports and hospital treatment.

The beliefs that fat or obese children are infection- and accident-prone and the products of over-solicitous and protective parents are frequently cited. The extent to which this might be true can be partially determined by an appraisal of Table XI, where the 39 fat-pad children are contrasted with the 50 control children. It is apparent that the two groups of children were not distinctly different in their illness experience. There was no pattern of illness which seemed to be common to either group.

The psychological evaluations of the two groups is admittedly very superficial. However, the percentages are of interest for comparison with those reported by Bruch.[29] Obese children are frequently characterized as physically inactive because they are clumsy, slow, and unable to defend themselves; socially immature because they are timid; retiring, over-sensitive, and frustrated because they cannot adequately deal with their environment. This did not seem to be true of the female fat-pad children studied, since they appeared to be as active and as friendly as the control group of children, and they exhibited no greater incidence of noxious habits than the latter. The fat-pad boys seemed to be somewhat less active, less friendly, and have fewer noxious habits than the control children. As was stated earlier, the more extreme cases of obesity were found in the boys, so it may be true that this group contained more children for whom oral satisfaction served as a means of compensating for emotional difficulties. By eating excessively, these boys may have exaggerated their size and at the same time found an emotional outlet, thereby reducing their play activities, their contact with other children, and the opportunity to develop psychological disturbances manifested as noxious habits. But this explanation, which is so frequently given for the behavior of obese children, is contradicted by the intensive investigation of their dietary habits. It was apparent from the study that the fat-pad children as a group did not overeat. The discrepancy found in the psychological evaluations has no adequate explanation at the present time.

The recent work of Reynolds[19] offers a possible explanation for the presence of fat pads in children who do not eat excessively, as he found that extreme skeletal breadth, rather than a distribution of subcutaneous fat, was responsible for trochanteric "bulges" in at least one of the Fels Research Institute subjects.

Further analyses indicate that there are only three high coefficients of correlation among the fat-pad boys and girls. These pertain to: (a) height and weight in boys; (b) systolic and diastolic blood pressures in boys; and (c) systolic blood pressure and protein intake in girls. The calculations which yielded figures that were not statistically significant are equally as important as those which did yield statistically significant figures, for they give strong indications of an absence of associations, or an absence of any one fundamental factor.

In reading this report it will be noticed that such words and phrases as "tend to," "seem to," and, "probable that" have been frequently used. This is a reflection of two factors: (a) The findings presented can apply only to the Forsyth fat-pad group, and no inferences about the boy-girl population of the United States as a whole should be drawn. (b) So little is known about obesity that we cannot speak with any precision about its causes.

If the present investigation could be continued into a longitudinal study, it is felt that this would give more evidence and a possible explanation of the growth processes of "fat" children as contrasted with "normal" children.

Summary

Of the 414 children included in the Forsyth Child Growth Program, 39 children (26 girls and 13 boys, ranging in age from 5 through 14 years) were selected for special investigation

on the basis of fat pads or folds in at least two of three body regions as seen in somatotype pictures. A control group of 50 children (26 girls and 24 boys, ranging in age from 4 through 14 years) was selected at random for comparative purposes.

Data were gathered and analyzed for a number of medical, anthropomorphic, and psycho-social variables.

Analysis of these data showed that:

Height and weight deviations were markedly dissimilar, with 95 per cent of the fat-pad group exceeding the age norms in weight, while only 59 per cent were comparably above the norms in stature. Tooth emergence data showed 72 per cent of the sample as advanced, and 65 per cent of the sample were advanced in bone age.

Of the fat-pad children beyond the prepuberal age, 56.5 per cent were advanced in sexual maturation.

Fat-pad boys and girls were significantly different in measurements of diastolic blood pressure. Fat-pad boys had significantly higher diastolic pressures than control boys. Systolic blood pressures were not found to be significantly different between fat-pad and control children or between boys and girls.

No real differences between the fat-pad and control children could be found in their mental and locomotor development. Only the fat-pad and control boys yielded a significant difference in age of eruption of deciduous dentition, with the control boys the earliest. The diets of fat-pad children were not excessive either in calories or fat-building substances; the Forsyth fat-pad group as a whole did not overeat. Familial background, social environment, ethnic origin, and a tendency to fatness in the mother were not found to be contributory factors. The fat-pad children came from smaller families than did the control children. A larger percentage of them than of the control children had, for a period of at least 7 years, been in the position of "baby" of the family. The weight gain of the mother during pregnancy, and the birth weight of the child do not appear to be associated with the development of obesity in the offspring.

Fifty per cent of the children selected on the basis of fat pads were considered obese on the basis of a medical evaluation, and 59 per cent of them consistently increased their percentile ratings of weight during the time they were observed. An examination of the illness experience of the two groups indicated no tendency for the fat-pad children to be more subject to infections or accidents than the control children. The fat-pad girls were found to be as active, as friendly, and exhibit no more noxious habits than the control children, whereas the fat-pad boys seemed somewhat less active, less friendly, and had fewer noxious habits than the other children.

Acknowledgments

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Resumen

Un estudio comparativo de niños "obesos" seleccionados en relación con depósitos adiposos

De 414 niños, 39 (26 muchachas y 13 muchachos), cuya edad oscilaba entre 5 y 14 años, se seleccionaron para una investigación especial basada en la presencia de depósitos adiposos por lo menos en 2 de 3 regiones del cuerpo, como se ven en los cuadros de tipo somático. Un grupo control de 50 niños (26 muchachas y 24 muchachos), cuya edad oscilaba entre 4 y 14 años, se seleccionó a la aventura con el objeto de comparación.

Los datos se reuniron y analizaron desde diferentes puntos de vista médicos, antropomórficos y psico-sociológicos.

Los análisis de estos datos mostraron:

Las deviaciones de talla y peso fueron marcadamente desiguales, con un 95 por 100 del grupo con depósitos adiposos excediendo las tablas normales de peso, mientras que solamente un 59 por 100 sobrepasaron en un grado comparable las normas de talla para su edad. Los datos referentes a la aparición de los dientes demostraron que un 72 por 100 fueron precoces, y un 65 por 100 fueron precoces en edad osea.

De los niños con depósitos adiposos que se encontraban en la edad prepuberal, 56,5 por 100 mostraban una maduración sexual avanzada.

Los muchachos y muchachas adiposas mostraron diferencias importantes en las cifras de la tensión arterial diastólica. Estos muchachos presentaban presiones diastólicas mayores que las de los muchachos control. En cambio, no se encontraron diferencias mayores en la presión sistólica entre los niños adiposos y control, ni entre muchachos y muchachas.

Ninguna diferencia verdadera entre los niños adiposos y control se hallaron en cuanto a su desarollo mental y locomotor. Solamente los muchachos adiposos y control revelaron una diferencia importante en la edad de erupción de la primera dentición, siendo los niños control los más precoces. Las dietas de los niños adiposos no fueron excesivas ni en calorías ni en substancias lipógenas: el grupo, en su totalidad, no comía demasiado. El ambiente familiar y social, el origen étnico, y la

tendencia a la gordura en la madre no se encontraron ser factores contribuyentes. Los niños adiposos eran descendientes de familias más pequeñas que las de los niños control. Un porcentaje mayor de aquellos había sido, durante un período de 7 años por lo menos, el "niño mimado" de la familia. El aumento ponderal de la madre durante el embarazo, y el peso del niño al nacer, no parecen asociados al desarollo de la obesidad en los niños.

El 50 por 100 de los niños seleccionados a causa de los depósitos de grasa fueron considerados obesos en la base de un examen médico, y el 59 por 100 de ellos aumentaron regularmente sus porcentajes medios de peso durante el período de observación. Una investigación de la historia patológica de los 2 grupos demostró que no existía en el grupo adiposo ninguna predisposición mayor para infecciones o accidentes que en los niños control. Las muchachas adiposas eran tan activas y amigables como las muchachas control, y no mostraban mas hábitos nocivos que estas. Los muchachos adiposos, al contrario, parecían algo menos activos y menos amigables y tenían menos hábitos nocivos que los demás niños.

Editorial

Aging, Malnutrition, and Hormones

The processes of aging are intimately concerned with nutrition. Good nutrition slows and poor nutrition accelerates the processes of physiologic aging. There are many controlled scientific studies and much clinical observation to support this concept.

In starvation actual aging processes in tissues become apparent. Malnourished or starved persons may rapidly assume the appearance of advancing years; the hair may lose its color and become thin, the skin wrinkled and inelastic. Sexual functions wane, and bone, muscle, and vital glands and organs may develop microscopic and chemical changes typical of so-called senile degeneration. In prolonged nutritive failure from any cause—whether inadequate intake, failure of absorption or utilization, excessive elimination or abnormal loss, or increased metabolism and toxic destruction—actual aging of tissues as well as apparent aging may take place. In extreme cases of anorexia nervosa the rapid development of practically all the attributes of senility may be striking, and may in fact result in death. Much emphasis has of late been quite properly placed upon the higher death rates attributable to obesity. Equal emphasis should be directed to the evidence that optimum nutrition (which includes the concept of avoiding corpulence) prolongs life.

Elderly persons suffer from nutritive deficiency often because of the frequency with which economic, psychological, and organic problems beset them. In the higher decades one must be on guard not to accept degenerative changes as the inevitable erosion of the years. Often generation, growth, and repair are still possible, often *de*generation can be retarded—by improvement in nutrition. One of the great advances in modern medicine is the recognition that many changes which were previously thought to be inescapable consequences of advancing years are reversible or preventable, or at least postponable.

Actually a new meaning of senescence has arisen. It now means the degeneration of advanced age, but we do not accept it as the unavoidable accompaniment of longevity.

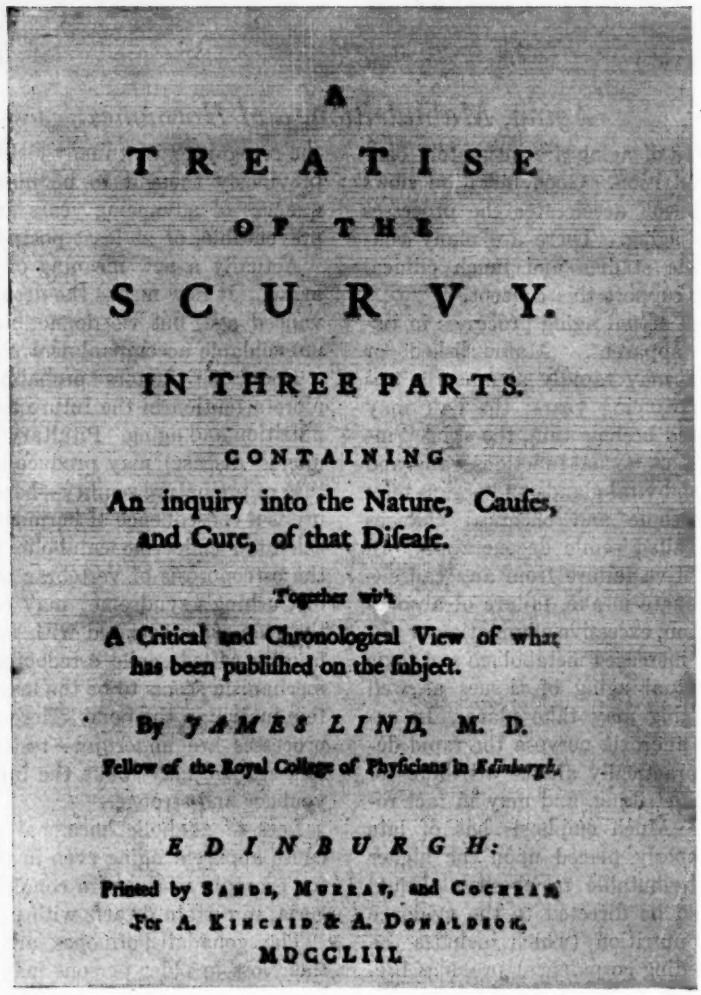
Endocrine factors probably will receive more attention in the future as they relate to nutrition and aging. Pituitary cachexia (Simmonds' disease) may produce the perfect picture of premature senility—here nutritive failure is a consequence of hormonal failure. Accelerated endocrine catabolic processes (e.g., the osteoporosis of vertebrae and other bones of Cushing's syndrome) may closely simulate the changes associated with aging which are usually called senile osteoporosis. The chief mechanism seems to be the loss of a good protein matrix in the bone. Here again nutritive processes are important—restoration of protein storage may make the bones apparently younger and stronger.

Loss of anabolic hormonal influences may cause apparent aging even in the very young, for example in the rare condition called progeria, in certain dwarfs with pituitary failure.

The gonadal hormones are anabolic and their loss in older persons may be one of the causes of senescence. Premature loss of estrogen or testosterone is known to cause fine wrinkling, loss of hair, and other overt manifestations of aging. Recent experimental studies suggest that hormone therapy may retard senescence.

Nutrition and hormones, closely interrelated, may provide the means for man's further experiments into the benefits of longevity.

—Cyril M. MacBryde, M.D.


A

TREATISE

OF THE

SCURVY.

IN THREE PARTS.

CONTAINING

An inquiry into the Nature, Cauſes, and Cure, of that Diſeaſe.

Together with

A Critical and Chronological View of what has been publiſhed on the ſubject.

By JAMES LIND, M. D.

Fellow of the Royal College of Phyſicians in Edinburgh.

EDINBURGH:

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MDCCLIII.

(Courtesy of the University Press, Edinburgh)

Title page of the first edition of Lind's "Treatise of the Scurvy."

1753
LIND, LEMONS AND LIMEYS

By S. O. WAIFE, M.D.

IN 1753, just 200 years ago, Samuel Johnson was busy with his dictionary, George Washington obtained his first military commission, and a short book appeared which, in its way, was to revolutionize the world. Much of future history was to involve exploration, maritime trade, and colonial expansion. These developments could occur in part only because "the great sea plague" was finally conquered. And this nautical scourge—scurvy—was overcome largely through a brilliant model clinical experiment by a Scotsman serving as a surgeon in the Royal Navy.

It is difficult for us in these halcyon days of ascorbic acid to appreciate the problem faced each winter by the scurvy-ridden population of Europe in the pre-Lind era, the perplexity of Hippocrates confronted by large numbers of soldiers suffering from pains in the legs and gangrene of the gums, or the remarks of de Joinville regarding a 13th-century crusade in which barber surgeons had to "cut away the dead flesh from the gums to enable the people to masticate their food."[1]

Several monographs on what we now assume was scurvy appeared soon after the printing press became active, and, in fact, in 1645 the Faculty of Medicine at Copenhagen published a summary of their knowledge of this prevalent syndrome. The earlier settlers in Hudson Bay were forced to discontinue their colonization of the region because of scurvy, while in 1703, during a siege of the town of Thorn in Prussia, an epidemic of scurvy killed 5000 of the garrison and many civilians.

In many places on the globe, in Russia, India, Africa, and the United States, epidemics occurred among troops, in prisons, asylums, and homes for the indigent. The year 1753 did not bring an end to all this, for in the War Between the States, over 100 years later: "Among the white troops during the five and one-sixth years covered by the statistics, 30,714 cases of scurvy were reported; and 383 deaths were attributed directly to that disease." In the Franco-Prussian War (1870–71) scurvy was prevalent in the besieged city of Paris. In the Russo-Japanese War, half the garrison of 17,000 men at Port Arthur had scurvy. As recently as World War I a unit of 100 beds per division in the Russian Army was set aside for scurvy, while 11,000 cases were reported from the Indian troops in six months in 1916. (It should be noted that only 20 cases of scurvy were reported among all American troops in 1917 and 1918.)

Let us jump back to 1496, when Vasco da Gama's ships sailed to India. The Portuguese poet Camoens wrote:[2]

A dread disease its rankling horrors shed
And death's dire ravage through mine army spread,
Never mine eyes such dreary sight beheld,
Ghastly the mouths and gums enormous swelled
And instant, putrid like a dead man's wound,
Poisoned with fetid streams the air around.
No sage physician's ever watchful zeal,
No skilful surgeon's gentle hand to heal
Was found, each dreary mournful hour we gave
Some brave companion to a foreign grave.

This killer is said to have claimed almost all of Magellan's crew, and when Anson sailed around the world in 1740–44 nearly two-thirds of his crew of men died of scurvy. A naval surgeon in the Napoleonic Wars wrote: "it is the opinion of some of the most experienced officers that the blockade system of warfare

From the Lilly Research Laboratories and Indiana University Medical Center, Indianapolis.

which annihilated the naval power of France could not have been carried on unless sea scurvy had been subdued."

Was, then, this book, whose two-hundredth anniversary we celebrate this year, the first that explained how scurvy could be controlled? It is a commentary on man's reception of new ideas that over 100 years before (1636) the first naval surgeon, John Woodall, wrote:[3]

"The juyce of lemmons is a precious medicine and well tried; being sound and good let it have the chief place, for it will deserve it, the use whereof is: It is to be taken each morning two or three spoonfulls, and fast after it two hours. Some chirurgeons also give of this juyce daily to the men in health as a preservative."

And Shakespeare's son-in-law, Dr. John Hall, cured scurvy by brewing a beer or ale of "ascorbutic herbs, viz.: scurvy grass, watercresses and brook lime."

What, then, is the significance of 1753? In that year appeared "A Treatise of the Scurvy in three parts. Containing An inquiry into the Nature, Causes, and Cure, of that Disease. Together with a A Critical and Chronological View of what has been published on the subject" by James Lind, M.D., Fellow of the Royal College of Physicians in Edinburgh.[4]

James Lind, a pioneer in clinical nutrition experimentation, was born in 1716 and died 78 years later, the respected head of the Royal Naval Hospital at Haslar. Although he deserves full honor for his recommendations on personal cleanliness, hygiene, and sanitation, which really began the science of naval medicine, and for his studies of tropical preventive medicine, he is best known for his report of a simple experiment on board the H.M.S. *Salisbury* in 1747.

Lind selected 12 scorbutic sailors from the many on board. These men were as alike as possible in regard to symptoms and physical condition. He then tested simultaneously the various therapies in common use at that time. Six groups of two men each were formed. In addition to the usual rations, one group received a quart of cider a day, another 25 drops of an elixir of dilute sulfuric acid three times a day and a mouth wash of this preparation. Similarly, other groups received vinegar, sea water, and a pill containing garlic, radish, mustard seed, and the like. One group of two men had a lemon and two oranges daily.

Within a week these last two recovered to such an extent that one man returned to duty, while the other acted as nurse for the other ten, whose condition scarcely changed.

This study was well planned and concise, and even according to modern advanced ideas on scientific research, it was a well-controlled experiment. Lind's clear statements of his careful observations leave no question as to the importance of the findings.

Here, then, was a clinical experiment which should have established beyond doubt the efficacy of lemons and oranges in the treatment and prevention of scurvy. This is doubly to be expected because Lind's work was "proof" of what had been known for some time, in some quarters at least. For there are letters from early New England settlers, one hundred years before Lind, stating that lemon juice speeded the recovery of scorbutics, and Scott[3] mentions that a Dutch physician, Ronssens, wrote in 1564 that "Dutch sailors who, returning from Spain, were attracted by the novel richness of the fruit (oranges) and by their greed and gluttony unexpectedly drove out the disease (scurvy) and had this happy experience not on a single occasion only, but repeatedly."

However, it took fifty years and other naval surgeons to make this knowledge of practical value. Like other bureaucracies, the Admiralty was not receptive to change. In 1793, Dr. John Harness, a surgeon to the Mediterranean Fleet, was able to get the Admiral, Lord Hood, to order lemon juice to be supplied to all ships, with a consequent rapid decrease in the incidence of scurvy. This event, plus the fact that he was acquainted with the work of Lind, led Sir Gilbert Blane, a physician and administrator, to convince the First Lord of the Admiralty, Lord Spencer, to make lemon and other citrus fruit juices a requirement for all vessels of the Royal Navy. This was in 1795. Two years later, Lord Spencer found not one case of scurvy at the Royal Naval Hospital, whereas previously

there were always numerous cases to be found. (It is also of interest that Blane recognized that heating lemon juice reduced its antiscorbutic property, while adding a little sugar or spirits helped retain it.)

This story could not end without an ironic twist. Dr. James Lind died in 1794, a year *before* lemon juice was officially approved by the Admiralty.

In spite of the demonstration by Lind and others during various expeditions of the antiscorbutic property of lemon juice, it took a generation for official naval action. It took even longer for the merchant marine. And for many years after scurvy had been eradicated from the navy, it still appeared among the crews of commercial ships sailing to India, Ceylon, and China.

Even then, British sailors were not forever freed from the danger of scurvy. In 1850, political pressure forced the British Navy to stop using Mediterranean lemons as antiscorbutics and switch to Jamaican limes. These, unfortunately, contained little or no ascorbic acid. The use of limes led to the name "limey" as a synonym for the British sailor. It also led to disaster for the men of the Nares expedition to the North Pole, where, despite their consumption of large amounts of lime juice, many of the explorers died of scurvy. Because of this debacle, physicians, explorers, and sailors distrusted the value of citrus fruits as antiscorbutics, and there was a temporary return to the belief that scurvy was due to constipation and auto-intoxication.

Gradually, however, even the merchant marine realized the power in the lowly lemon, and ultimately, as we all know, scurvy was to all intents and purposes eliminated as a disease of mankind.

If there is a moral in this example of the slow recognition of a scientific achievement, there is also the corollary moral that good clinical experimentation requires simple tools, a clear head, and a courageous heart.

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1953

LIND BICENTENNIAL CELEBRATIONS IN EDINBURGH

By A. P. MEIKLEJOHN, M.D.

THE TWO-HUNDREDTH anniversary of the first publication of Lind's classic *Treatise of the Scurvy* was celebrated appropriately on May 22nd and 23rd in his home town, Edinburgh, Scotland, where he wrote the book after his retirement from active service in the British Royal Navy, and before he became chief physician to the largest hospital in Europe—the naval hospital at Haslar, outside Portsmouth.

The celebrations began with a ceremony arranged by the University of Edinburgh, in the 18th-century University library designed by the Adam brothers. The Vice-Chancellor, Sir Edward Appleton, one of Britain's leading physicists, presided, and conferred the honorary degree of LL.D. on Surgeon Vice-Admiral Sir Sheldon Dudley, R.N. (Ret.), who was Medical Director General of the Royal Navy from 1941 to 1945. Sir Sheldon then gave an oration in praise of Lind—a fighting speech, by a sailor about a sailor. Like Lind, Sir Sheldon has devoted his life to "preserving the health of sailors" and no one, perhaps, is so well qualified to assess Lind's reputation as "the father of nautical medicine." Sir Sheldon emphasized that the conquest of scurvy was by no means the only outcome of Lind's pioneering work in naval hygiene. His remarkable versatility was a lesson for the narrow specialists of today; several other lessons he taught had to be relearned by the navies of the Second World War. Professor R. C. Garry (Glasgow) as President of the Nutrition Society then presented two specially-bound copies of the reprint of Lind's book*—one for the Chancellor of the University, H.R.H. The Duke of Edinburgh, and one for Sir Sheldon. The ceremony concluded with the presentation to Lind's own University of Edinburgh of a handsome bronze plaque, bearing a portrait of Lind and a well-chosen inscription. The presentation was made by Dr. C. Glen King (New York) on behalf of the donors, the Sunkist Citrus Fruit Growers Association of California.

A two-day conference of the Nutrition Society followed, devoted to various aspects of scurvy and ascorbic acid. This was opened by Sir Edward Mellanby, the retired Secretary of the (British) Medical Research Council, who recounted his personal recollections of early vitamin research in Britain. He was followed by Dame Harriet Chick (London) who traced the history of scurvy from before Lind's time to the work at the Lister Institute which led up to the isolation of vitamin C. Dr. C. Glen King (New York) described the actual isolation (in which he himself played a leading part), the unraveling of the chemical nature and the synthesis of the vitamin, with an outline of work still in progress in his laboratory, on the origin of the vitamin in nature.

The afternoon session, presided over by the present Director General of the Royal Navy, Surgeon Vice-Admiral Sir Alexander Ingleby-Mackenzie, R.N., began with a paper by Dr. M. van Eekelen (Leyden, Holland) on dietary sources of ascorbic acid, in which he em-

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* *Lind's Treatise on Scurvy*, a Bicentenary Volume, being a reprint of the 1st Edition with additional Notes. Edited by C. P. Stewart and D. Guthrie, The University Press, Edinburgh, 1953.

phasized the dangers of scurvy in infants fed on heated or dried cow's milk, without proper vitamin supplements. Professor H. A. Krebs (Sheffield, England) described the experiment carried out in Sheffield during the recent war (and shortly to be published in full) in which the onset and course of scurvy was studied in volunteer conscientious objectors. The histology of scurvy was described in a paper contributed by the leading authority on the subject, Dr. S. Burt Wolbach (Boston). Dr. A. P. Meiklejohn (Edinburgh), in presenting his paper for him, reminded the audience of his great contribution to the study of diseases affecting connective tissue.

The meeting then adjourned from the University in the "Auld Toon," across Princes Street, to the "New Town" premises of the Royal College of Physicians, where the guests were welcomed by Dr. W. A. Alexander, President of the College of which James Lind was a Fellow and, for a time, Treasurer. He introduced Dr. V. P. Sydenstricker (Augusta, Ga.) who delivered the second Sydney Watson Smith Lecture, in which he gave a scholarly review of the history of vitamin research in relation to Medicine.

On the second day the Chairman for the opening session was Professor R. C. Garry (Glasgow), the retiring President of the Nutrition Society. The first paper was presented by Dr. John H. Crandon (Boston), the first man to have successfully induced scurvy in himself and survived. With objective humility he described the symptoms of the disease, from personal experience, and thereafter gave an account of his recent work on the ascorbic acid needs of surgical patients. Dr. Robert M. Kark (Chicago) followed with a paper in the true Lind tradition—skeptical of contemporary hypothetical guesswork. His own observations led him to doubt whether human requirements for ascorbic acid were increased by physical exertion, exposure to cold or stimulation of the adrenal cortex. Professor E. J. Bigwood (Brussels, Belgium), the former Chairman of the first League of Nations Technical Commission on Nutrition, gave an interesting paper on the urinary excretion of amino acids in ascorbic acid-deficient infants. The morning session ended with a paper by Dr. C. P. Stewart (Edinburgh) on the occurrence of dehydro-ascorbic acid in human blood plasma, and the relationship of this to hormones of the adrenal cortex and of the possible role of glutathione in this relationship.

At the final session the Chair was taken by Dr. L. J. Harris (Cambridge, England), the newly-elected President of the Nutritional Society. Dr. C. P. Stewart (Edinburgh) read a paper contributed by Mr. A. J. Lorenz (Los Angeles) giving a stimulating account of the early, pre-Lind writings on scurvy. Dr. H. Gounelle (Paris, France), in the delightful French manner, presented his observations on ascorbic acid deficiency during the recent war and after; he particularly stressed the large doses of the vitamin that he had found necessary to obtain saturation in tuberculous prisoners-of-war. The next speaker was Dr. W. J. Darby (Nashville) who ably reviewed the current literature on ascorbic acid in relation to tyrosine metabolism and erythropoietic factors. Drs. L. W. Mapson and F. A. Isherwood (Cambridge, England) followed with an account of their work on the synthesis of ascorbic acid by plants and animals. Dr. L. J. Harris then led a discussion which served to emphasize the differences of opinion that still exist on the true requirements of man for ascorbic acid.

The celebrations ended with a light-hearted dinner at which Scurvy Grass (*Cochlearia offinalis*) appeared as a garnish for the fish and a new savory dish was introduced—Croûtes Szent-Györgyi—the proper recipe for which is adrenal glands on toast, garnished with paprika. Dr. C. P. Stewart proposed the toast of "The Memory of James Lind" which was replied to in fine spirit by Surgeon Rear-Admiral J. Hamilton, R.N., the present holder of Lind's position at Haslar Hospital.

The papers presented at the celebrations are to be published in a forthcoming special number of the *Proceedings* of the Nutrition Society. Becomingly, then, if belatedly, Lind receives his due.

Dietotherapy

LIQUID DIETS

By CORINNE H. ROBINSON*

LIQUID DIETS may be employed postoperatively, in febrile states, or in any situation where the patient is unable to tolerate solid foods. Because the diets are usually used for short periods of time, too little consideration is sometimes given to planning for nutritive adequacy.

The following are some formulae of liquid diets which have proved valuable in our experience and are offered as guides to the general use of such diets in practice. Naturally, in every case there will have to be modifications to tailor the nutritional intake to the patient's specific medical problem.

CLEAR LIQUID DIET

The clear liquid diet supplies fluid in the form of fat-free broth, ginger ale, tea and coffee with sugar but without milk or cream. The caloric intake will depend upon the quantity of ginger ale and the amount of sugar used in the tea or coffee, but in any case it will be insignificant in relation to total body needs. Occasionally, small amounts of strained fruit juices, egg white, and gelatin may be included on the clear liquid diet.

FULL LIQUID DIET

The full liquid diet includes all foods which are liquid at room temperature and at body temperature. It provides normal allowances of all the nutrients in a form which requires minimum activity for digestion and absorption. A guide for planning this diet follows:

Include these foods, or their equivalents, daily:

6 cups milk
2 eggs
½ cup strained cooked cereal for gruel
¼ cup vegetable purée for cream soup
1 cup citrus fruit juice
½ cup tomato or vegetable juice
1 tablespoon cocoa
3 tablespoons dried brewers' yeast
3 tablespoons sugar
1 tablespoon butter
2 servings plain gelatin dessert, Junket, custard, ices, or plain ice cream
Broth or bouillon

Nutritive values of foods specified above: Protein, 87 Gm.; calories, 1980; calcium, 2.1 Gm.; iron, 11 mg.; vitamin A, 6300 I.U.; thiamine, 3.3 mg.; riboflavin, 4.6 mg.; niacin, 12 mg.; ascorbic acid, 160 mg. *Note:* Failure to include brewers' yeast in the amounts specified will result in iron and niacin intakes below the recommended dietary allowances for adults in health.

To increase caloric level: (a) substitute light cream for part of the milk; (b) use glucose in fruit juices; (c) use ice cream for dessert or in beverages; and (d) use butter in soups and gruels.

To increase the protein level: (a) use nonfat milk solids in milk beverages,[1] custards, and cream soups; (b) use egg white with fruit juices; (c) add beaten whole egg to broth.

Meal Plan. Six or more feedings should be used daily. One way in which the above list of foods may be incorporated is given here:

Suggested Meal Pattern	*Sample Menu*
Breakfast	
Citrus juice	Orange juice
Cereal gruel with butter, sugar, milk	Strained oatmeal with hot milk, butter, sugar
Beverage with cream, sugar	Coffee with cream, sugar

*Head, Dept. Food and Nutrition, Drexel Institute of Technology, Philadelphia, Pa.

Midmorning	
Eggnog or Fruit juice with egg or Milk beverage	Malted milk
Noon Meal	
Strained soup	Cream of asparagus soup
Tomato juice with brewers' yeast	Tomato juice with yeast
Custard, ice cream, plain gelatin, or junket	Baked custard Milk
Eggnog, milk, or cocoa Tea or coffee, if desired	Tea with sugar, 1 lemon
Midafternoon	
Same as at midmorning	Ginger ale and grape juice with egg white
Evening Meal	
Strained soup	Beef broth with egg*
Citrus fruit juice	Grapefruit juice
Custard, ice cream, plain gelatin, or junket	Junket
Eggnog, milk, or cocoa	Hot chocolate made with milk
At Bedtime	
Same as at midmorning	Eggnog with vanilla ice cream

* To prepare broth with egg, add 2/3 cup hot broth gradually to one slightly beaten egg, stirring continuously. Serve at once.

Tube Feedings

Any foods which will pass easily through a tube may be used for a tube feeding. The selection of kinds and amounts of food is dependent upon the needs of the individual patient. Since these feedings may be needed for a long period of time, it is essential that all of the nutritive essentials be included. This is more readily accomplished when a formula, such as the one described below, is used.

High Protein Tube Feeding

	Household Measure	*Weight Gm.*
Skim milk	6 cups	1440
Nonfat milk solids	1 1/2 cups	150
Eggs	4	200
Sugar	1/2 cup	120
Molasses	1/2 cup	120
Brewers' yeast	3 tablespoons	25
Salt	1 teaspoon	5
Cod-liver oil or A and D concentrate	1 teaspoon oil	4

To prepare: Put skim milk in large bowl. Sprinkle milk solids on top of milk, and beat with rotary beater until well blended. Beat eggs, add sugar and molasses, and add gradually to milk, stirring until well mixed. Add yeast, oil, and salt; beat until smooth. Store in covered bottles in refrigerator.

To feed: Heat enough formula for one feeding over hot water. The formula should not be heated warmer than 100° F. since curdling may otherwise take place. Usually 6 to 8 ounces of this formula may be given at intervals of two to three hours.

Nutritive value of recipe: Protein, 143 Gm.; calories, 2309; calcium, 4.2 Gm.; iron, 23 mg.; vitamin A, 6500 I.U.; thiamine, 3.9 mg.; riboflavin, 7.8 mg.; niacin, 15.6 mg.; ascorbic acid, 14 mg.

Ascorbic acid is provided by giving 3/4 cup orange juice by tube daily.

Variations: To increase calories, use whole milk in place of skim milk. To increase protein, use Casec® in place of nonfat milk solids. If there is a tendency to diarrhea, add apple sauce or apple powder to the formula.

REFERENCE

1. Robinson, C. H.: Planning the high protein diet. J. Clin. Nutrition 1: 401, 1953.

Nutrition Briefs

CURRENT OBSERVATIONS OF CLINICAL INTEREST

IF MILK IS treated with Florisil®, a synthetic magnesium silicate compound, over 90 per cent of the riboflavin and thiamine in milk will be removed. This would be useful in planning palatable experimental diets low in these two vitamins.

L. F. Adamson. *Science* 117: 253, 1953.

IN SPITE OF A lysine-deficient diet, 6 infants had normal plasma proteins. There was evidence that another amino acid, arginine, substituted for lysine in the protein.

A. A. Albanese. *J. Biol. Chem.* 200: 787, 1953.

A DIET devoid of fat markedly predisposes to the development of toxic effects of vitamin A on doses ordinarily nontoxic or only mildly toxic.

T. C. Panos and J. C. Finerty. *Fed. Proc.* 12: 399, 1953.

HUMAN pellagra following "wheat" or "corn" diets containing about 200 mg. of tryptophane can be prevented by as little as 5 to 7 mg. of niacin daily.

G. A. Goldsmith, H. L. Rosenthal, and W. G. Unglaub. *Fed. Proc.* 12: 415, 1953.

CHILDREN with cystic fibrosis of the pancreas, celiac syndrome, and other conditions associated with faulty fat absorption have erythrocytes which hemolyze when incubated with hydrogen peroxide. This can be reversed by feeding *dl*-alpha-tocopherol acetate.

H. H. Gordon, R. H. Davis, and K. Morganstein. *Fed. Proc.* 12: 415, 1953.

HEPATOLENTICULAR degeneration in man has histopathologic changes resembling chronic manganese poisoning. Rats fed manganese chloride developed certain biochemical and morphologic changes resembling this disease.

C. J. Gubler *et al.* *Fed. Proc.* 12: 415, 1953.

ANALYSES of muscle and viscera for vitamin E in a fatal case of progressive muscular dystrophy revealed an adequate supply of tocopherol in muscle.

K. E. Mason, M. Y. Dju, and S. J. Chapin. *Fed. Proc.* 12: 422, 1953.

LIVER dysfunction developed in men kept on a protein-deficient diet for over a year. Supplementation with lysine, or methionine and choline or 10 Gm. of lactalbumin were ineffective. Thirty Gm. of lactalbumin or a "normal" diet adequate in protein was curative.

M. K. Horwitt, W. S. Rothwell, and R. M. Kark. *Fed. Proc.* 12: 417, 1953.

ANALYSIS of army messes showed that an average of 2600 calories a day was consumed, composed of 102 Gm. protein, 259 Gm. carbohydrate, and 134 Gm. fat. With food consumed outside of mess halls, the average intake was 3300 calories per day.

W. J. Kuhl, Jr., W. R. Best, and C. F. Consolazio. *Fed Proc.* 12: 419, 1953.

THE MILK intake of pupils in a residential school was tripled (8 to 24 oz.). Over a two-year period certain vitamin deficiencies were dramatically reduced, respiratory infections decreased, and better school performances and more energy were noted.

L. B. Pett. *Fed. Proc.* 12: 426, 1953.

AN INTAKE of 40 mg. per day of ascorbic acid was needed to replete the vitamin C content of the white cells after induced deficiency in normal persons.

B. F. Steele, R. Liner, Z. H. Pierce, and H. H. Williams. *Fed. Proc.* 12: 430, 1953.

RECENT ADVANCES IN EXPERIMENTAL NUTRITION

VITAMIN B_{12} increased the growth and tissue deposition of vitamin A in rats fed limited amounts of carotene.

E. G. High and S. S. Wilson. *J. Nutrition* 50: 203, 1953.

PENICILLIN increased the efficiency of feed utilization at all levels of protein investigated, producing a definite and consistent growth response.

H. C. Saxena, M. E. Starr, L. G. Blaylock, J. S. Carver, and J. McGinnis. *Arch. Biochem. & Biophys.* 44: 346, 1953.

DIETS which ordinarily produced a fatty liver did not have this effect if the experimental animals were deprived of pantothenic acid. There was evidence that in pantothenic acid deficiency adrenal hormone production is depressed and fat metabolism is altered. Transport of fat to the liver is prevented as a result of this deficiency.

A. F. Morgan and E. M. Lewis. *J. Biochem.* 200: 839, 1953.

FOLIC ACID-depleted rats much more frequently showed bacteremia from endogenous infection (*E. coli, staphylococci,* etc.) than did control animals.

C. F. Asenjo and A. Pomales-Lebrón. *Fed. Proc.* 12: 409, 1953.

RABBITS during vitamin E deficiency showed an increase in amino acids in the urine, as well as in creatinuria. Vitamin E also hastened the appearance of Vitamin B_6 deficiency symptoms when fed with a pyridoxine-deficient diet.

J. S. Dinning. *Fed. Proc.* 12: 412, 1953.

MALE ANIMALS on a high fat diet showed a significantly shortened life span when compared to average or high carbohydrate fed animals. No changes in longevity were noted among the females.

C. E. French *et al. Fed. Proc.* 12: 414, 1953.

THE RATE of oxidation of alcohol is dependent on the amount administered. Fasting markedly decreases the rate of oxidation.

D. M. Hegsted, J. J. Vitale, and J. Di Giorgio. *Fed. Proc.* 12: 416, 1953.

EXPERIMENTS in dogs with various ligated sections of the intestine show that vitamin B_{12} is absorbed primarily in the duodenum and not in the stomach.

H. L. Rosenthal and J. K. Hampton, Jr. *Fed. Proc.* 12: 428, 1953.

LARGE DOSES of cortisone to rats impaired the conversion of carotene into vitamin A.

I. Clark and R. W. Colburn. *Fed. Proc.* 12: 190, 1953.

BOTH vitamin B_1 and vitamin B_2 stimulated seed germination, but when the two vitamins were added to the culture together germination was distinctly retarded, both as to time and velocity of growth. This inhibition was marked by diminished absorption of water and reduced biosynthesis of protoplasmic substances. Both of these activities were greatly increased and growth was accelerated when either vitamin was given singly.

—G. Di Maggio. *Acta vitaminol.* 6: 159, 1952.

IN EXPERIMENTAL chronic CCl_4 intoxication in rats, daily oral treatment with 8 mg. of vitamin E delayed and minimized the occurrence of hepatic cirrhosis. As compared to the control group, in which precirrhotic symptoms and even true cirrhosis were found, vitamin E-treated rats showed only minor hepatic lesions (steatosis and necrosis) and none developed true hepatic cirrhosis.

—I. Moretti. *Acta vitaminol.* 6: 163, 1952.

RATS suffering from vitamin B_6 deficiency showed an impaired ability to utilize ingested nitrogen. They also showed an increase in fasting blood urea but no evidence of anemia or change in blood sugar and amino-nitrogen levels.

J. R. Beaton, J. L. Beare, J. M. White, and E. W. McHenry. *J. Biochem.* 200: 715, 1953.

HAMSTERS on an almost fat-free diet developed a profuse secretion of cerumen on the tympanic membrane. This could be prevented by feeding fat or small amounts of linoleic acid.

F. Christensen and H. Dam. *Acta physiol. Scandinav.* 27: 204, 1952.

Body Composition in Old Age

"An interesting aspect of nutritional change in old age is the shift in body composition. By and large, leanness has been considered a natural and desirable physiologic attribute of aging. Nevertheless, many older people develop more or less obesity with all the well-known consequent disadvantages. Furthermore, and of possibly even greater significance from the viewpoint of fundamental processes of nutrition in the aging, Brožek and Keys have shown that despite the maintenance of body weight at a constant 'normal' level, the proportion of fat to total tissue increases with age until in older men it may amount to as much as 22 per cent compared to approximately 10 per cent in younger men."

—J. B. Youmans. *Journal of the American Dietetic Association* 28: 1032–1033, 1952.

Nutritional Quotes

Iron Preparations

"There are hundreds of mixtures containing iron, but most of them are expensive and relatively inefficient. If they contain liver, hog stomach, or folic acid, and the anaemia proves refractory, they destroy many of the clues on which the haematologist depends. Iron-deficiency anaemia can best be cured by administering by mouth iron as a simple ferrous salt, and the only adjuvant of real value is ascorbic acid. Occasionally intravenous injections are desirable, if absorption is poor, or the patient is sensitive to iron; but these occasions are rare. . .

"Most patients tolerate iron well if it is carefully administered. It is essential to start treatment with a small dose, and to increase it slowly; massive dosage often causes ugestive upsets and should be avoided. Every dose should be taken in the course of a meal containing a reasonable amount of protein, and if massive doses must be used, they should be proportional to the size of the meal."

—G. Discombe. *The Medical Press* 229: 329, 330, 1953.

Effects of Fluorine Intake

"In human nutrition, the physiologic effects of fluorine are largely exerted through the drinking water, though there are some high-fluorine foods that may contribute significant amounts to the day's intake of fluorine, which generally, without undue exposure to fluorine, amounts to 0.3 to 1.5 mg. per day. At such low levels of consumption little retention occurs, but definite retention may occur at 4 to 5 mg. fluorine daily and perhaps at lower levels. The fluoride contained in waters carrying 1.0 to 1.5 p.p.m. exerts a beneficial and marked effect in preventing or retarding dental caries (eufluorosis). At higher levels, the effect is harmful (dysfluorosis), leading to severe disturbance of the functions of the ameloblasts and of the odontoblasts of the teeth (chronic endemic dental fluorosis, or mottled enamel) and eventually to osteosclerosis and calcification of the ligaments and joint capsules. ... However, these effects are noticeable only after many years of exposure. It has been estimated by Machle and by Roholm that daily intakes of about 15 to 20 mg. fluorine, in the drinking water or in industrial exposure, over a period of several years is required to induce chronic fluorosis in an adult man."

—H. H. Mitchell and M. Edman. *Journal of the American Dietetic Association* 28: 27, 1952.

Adaptation to Undernutrition

"The recent experience during and following the war has served to emphasize and to clarify the body's rather remarkable powers of adaptation to undernutrition. One mechanism has already been described, that of temporarily lessened or delayed growth in children. For adults there are adaptive processes also. There is loss of weight, also occurring in children if the lack of food is sufficiently great. Weight loss alone is sufficient to reduce very materially the caloric requirements simply because of the reduction in bulk. An additional reduction in requirements is obtained from a lowered metabolic rate. A decrease in the caloric expenditure for physical exertion provides further savings, 40 per cent of which is in the direct energy cost, in direct proportion to loss of body weight. These reductions in metabolism and energy cost of exertion in turn lower the requirements of other nutrients, notably the B-complex vitamins."

—J. B. Youmans. *Journal of the American Dietetic Association* 28: 1034, 1952.

Diet in Renal Insufficiency

"We believe that a useful life is possible for patients with chronic kidney insufficiency as long as they are able to produce 1200 to 1500 ml. of urine per day, no matter how lacking in concentration. Some patients who have entered the hospital with severe renal failure and who were in deep uremia when put on the diet have returned to their homes and sometimes to work for a year or more. It is unlikely that this could have been accomplished by the management of the concomitant cardiac failure and water and electrolyte disturbances alone. Comparison of their general condition before and during the dietary regimen has led many patients to the conclusion that keeping on the diet is worth the trouble and that life without a steak for dinner has still a lot to offer."

—W. J. Kolff. *Nutrition Reviews* 11: 193, 1953.

Nutrition News

☆ *News of activities in the field of clinical nutrition should be submitted to the Editorial Office of the* JOURNAL.

AMERICAN BOARD OF NUTRITION

The American Board of Nutrition will hold certifying examinations in Atlantic City, New Jersey, during April 1954. Completed applications of persons wishing to be considered for certification should be in the office of the Secretary not later than February 1, 1954. Application forms may be obtained from the Secretary, Otto A. Bessey, Department of Biochemistry and Nutrition, The University of Texas School of Medicine, Galveston, Texas.

FLOYD S. DAFT

Dr. Floyd S. Daft has been appointed Director of the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md. Dr. Daft, Acting Director of the Institute since the resignation of Dr. Russell M. Wilder last June, had been assistant director and chief of laboratory research since 1951. He has been a member of the scientific staff of the National Institutes of Health, principal research arm of the Public Health Service, since 1937. He has directed and conducted nutrition studies, particularly on the B vitamins, and his investigations have contributed importantly to the understanding of dietary deficiencies causing anemia, cirrhosis of the liver, and other metabolic diseases. He was a pioneer in the study of an unidentified substance later shown to be folic acid, a vitamin used widely today in the treatment of blood disorders.

Before coming to the National Institute of Health in 1937 Dr. Daft taught and engaged in research work at Harvard, Yale, the Carlsberg Laboratories, Copenhagen, Denmark, and the University of Rochester. In June 1952, he was awarded the honorary degree of Doctor of Science by Simpson College, Indianola, Iowa, where he earned his undergraduate degree in 1921. He attained his doctorate at Yale in 1926.

Diet and Old Age

"There is little doubt that more signs of nutritional inadequacy may be found in older men than in younger individuals, but there is no reliable evidence to indicate that such deficiencies are due to an increased requirement of nutrients. The quest for food being less of a stimulating experience, there is a gradual deterioration in the will to extend oneself to prepare or seek a good diet. . . .

"The problem is not one of altered requirements, but rather of altered habit patterns which cause a decrease in the amounts of nutrients ingested. It is true that many older people are in poor nutritive state, but the recognition that these deficiencies are not due to different physiologic needs should prevent dosing with excess vitamins and proteins. Such nutrients when fed in excess must be metabolized, conjugated, and excreted, which provides work but no apparent benefit to the aging tissues."

—M. K. Horwitt. *Journal of the American Dietetic Association* **29**: 443, 447, 1953.

Reviews of Recent Books

B-Vitamins for Blood Formation by Thomas H. Jukes, Charles C Thomas, Springfield, Illinois, 1952, pp. 113, $4.00.

This is a brief summary of the role of B-vitamins in blood formation. The monograph is particularly valuable for the excellent summarization of the experimental studies involved in the discovery of folic acid and the vitamin B_{12} group of compounds and gives details concerning what is known of the chemical properties and metabolic aspects of these vitamins. The monograph also deals with the citrovorum factor, the "intrinsic factor," and, very briefly, with vitamin B_6. M.M.W.

Refining of Oils and Fats for Edible Purposes by A. J. C. Andersen, Academic Press, Inc., New York, 1953, pp. 204, $7.00.

This book, by a British chemical engineer, describes the methods of removal of fat-soluble and fat-insoluble impurities in the refining of oils and fats. The principles and practices of various treatments of degumming, deacidification, bleaching, deodorization, etc. are described. There are numerous illustrations and flow-diagrams showing machines that are in common use.

This is a book aimed for the chemical engineer or the industrial organization that actually processes these fats and oils for the preparation of edible material. It will be of interest to those concerned with the technical aspects of the procedures. A.E.S.

General Biochemistry by Joseph S. Fruton, Ph.D., and Sofia Simmonds, Ph.D., John Wiley & Sons, Inc., New York, 1953, pp. 940, $10.00.

This volume should interest any reader whose field impinges to any extent on that of biochemistry. The authors' approach to biochemistry is semihistorical, in that the reader first learns what was learned first about a given topic. The subject is then gradually expanded, the order of complexity paralleling the chronological order of biochemical progress. History and procedure, discovery and theory are carefully interwoven, until finally the reader is led to a consideration of the latest techniques and a summation of current knowledge.

Proteins are considered in the opening section; their classification, isolation, chemistry, behavior as electrolytes, linkages and interrelations with other substances are described. Comprehensive sections follow on enzymes, biological oxidation, and the intermediate metabolism of carbohydrates, lipids, and nitrogen compounds. A final section is devoted to general aspects of metabolism, including the role of vitamins, hormones, and inorganic ions. This material, so vital to the understanding of nutrition, is presented in a clear fashion. Recent work on the newer growth factors is covered, and the references are as up to date as the process of printing allows.

Since this is not a practical manual for laboratory use, the sections dealing with procedures are not precisely detailed; they are, however, clear and complete enough to guide the reader to a better understanding of their applications, results, and implications. References to more detailed descriptions of the methods discussed are conveniently available in the footnotes.

Mathematical techniques and the principles of physics are discussed wherever these are necessary to the understanding of dynamic organic processes. Kinetics and thermodynamics illumine the discussion of enzyme-catalyzed reactions, and the possibilities—and limitations—of isotope-tracer methods are considered.

The English language is handled unusually well—not always the case in technical works. Economy of style is achieved without sacrifice of necessary detail, and consideration of detail never interferes with the orderly and logical progression of the exposition.

Since almost every further discovery in biochemistry casts additional light on basic metabolic processes and supplies the physician and nutritionist with new experimental and clinical tools, a *summa* such as this should serve as a helpful refresher course and stimulating guide to workers in all related fields. C.-J.H.

Refrigeration in America. A History of a New Technology and Its Impact by Oscar Edward Anderson, Jr. Published for the University of Cincinnati by Princeton University Press, 1953, pp. 344, $6.00.

The author of this book, a university professor, has presented a very informative and exceptionally well-documented survey of the evolution of refrigeration, tracing it from earliest times through the year 1950 but with major emphasis on the diverse applications of refrigeration within the United States. It was the practical applications of refrigeration rather than the development of the scientific principles upon which these rest that are so uniquely American developments. In no other country have the applications of refrigeration been so highly developed nor produced such a profound impact on socio-economic aspects of national life.

There are included within this historical survey of refrigeration the outstanding developments in the specialized categories of the home food refrigerator, the cold storage warehouse, the refrigerated freight car, refrigeration facilities of merchant sea-going vessels, the frozen food industry, the community frozen food locker, and air-conditioning directed toward improving human comfort—along with sketches of the technical improvements which made progress in each of these fields possible.

Natural ice, harvested in the winter seasons from rivers, lakes, and ponds, was the first refrigerant of commercial importance. From primitive beginnings the natural ice industry grew steadily in volume and efficiency in this country until about 1860, continued in a strong position for some years, but fell into a decided decline by the first decade of the 20th Century. Meanwhile, a method of manufacturing ice had been discovered (about 1775) and came into greatest prominence in the southern part of the United States, reaching peak production in 1931.

Cold storage warehouses for food began to be in evidence during the mid-1850's and were definitely a commercial success by around 1875. Practical refrigerator cars used for the transport of dressed beef came into being around 1870 and were in fairly wide use by the meat-packing industry by 1890. The rapid advance of the industrial age, together with the growth of large urban centers, gave a tremendous stimulus to both cold storage and refrigerated transport of fresh foods. By 1950 cold storage warehouses were scattered across the entire country, with concentrations in regions of food production, in large urban centers, and at various intermediate positions. By 1950 there were at least 110,000 general service refrigerator cars in operation in the United States, with about 35,000 of these suitable for transport of fresh fruits and vegetables.

The spectacular advent of frozen foods for retail distribution began in the 1920's as more or less an outgrowth or progression of methods first developed in the fish industry. The rapid success in this area of food refrigeration was, in no small degree, attributable to the leadership of scientists associated with the United States Department of Agriculture. By 1950 the commercial frozen-fruit pack had reached the annual rate of 481,000,000 pounds, and frozen vegetables 587,000,000 pounds.

Air-conditioning, which had been successfully used in various manufacturing enterprises in the latter part of the 19th century, made its real beginning as a means of improving the comfort of people in the 1920's. The first large-scale users of air-conditioning for enhancing human comfort did so in hopes of increasing trade and profits . . . these included the motion-picture houses, followed by department stores, hotels, railroad passenger cars, ocean liners, motor buses, and offices. The chief obstacle to the wider use of air-conditioning in private homes continues to be the relatively high cost of installation.

It is clearly obvious that the manifold applications of the principles of refrigeration in the United States have exerted a tremendous impact upon socio-economic conditions. Our national dietary, as a result of modern food refrigeration, has become more varied, more nutritious, and more suited to the less active types of occupation accompanying the industrialization of the country. Modern refrigeration of foods has increased the possibilities of regional specialization in food production and of land-usage. The food resources of the entire country are now made available to all consumers within reach of good retail marketing facilities. The commercial "quick-freezing" of foods has resulted in changes in the varieties of fruits and vegetables grown in this country, with emphasis on varieties which provide the most acceptable frozen products. In large measure, food refrigeration has tended to stabilize food prices, eliminate glutting of the markets at respective peak seasons of harvesting, and provide further incentives to growers. Various refrigeration techniques have made possible the centralization of many food industries near centers of food production which has been attended with highly significant economies and less waste of by-products. Refrigeration has provided nursery-men and florists with means of retarding germination of seeds and bulbs at will, of delaying blossoming periods, and of holding cut flowers. The history of refrigeration in the United States has a dynamic background and shows no signs of slackening either in progressive development or impact.

For readers with specialized interest in some one phase of the evolution of refrigeration in the United States it may be something of a disappointment not to find that material already assembled as an uninterrupted story but rather scattered through the various chapters of this survey. However, such readers will undoubtedly be grateful for the inclusion of what would appear to be a very complete and usable index.

L.E.B.

Books received for review by the *Journal of Clinical Nutrition* are acknowledged in this column. As far as practicable those of special interest are selected, as space permits, for a more extensive review.

Biochemistry and Physiology of Nutrition. Vol. I, edited by G. H. Bourne and G. W. Kidder, Academic Press, Inc., New York, 1953, pp. 569, $13.00.

Hepatitis. Transactions of the International Society of Geographical Pathology, E. Karger A.G., Basel and New York, 1953, pp. 652, Swiss fr. 46.80.

Gourmet Cooking for Cardiac Diets by Florence Field, The World Publishing Co., Cleveland, 1953, pp. 350, $3.50.

Abstracts of Current Literature

ABSTRACTERS

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BREAST FEEDING

A new growth factor has been described in human milk which augments the growth of a strain of Lactobacillus bifidus. *This may account for the variation observed in bacterial flora produced by human milk as compared to formula feeding. It is possible that certain of the advantages claimed for breast feeding in infant nutrition may be attributable to the presence of this factor.*

A Hitherto Unrecognized Biochemical Difference Between Human Milk and Cow's Milk. P. György. *Pediatrics* 11: 98, 1953.

One of the major preoccupations of nutritionists and pediatricians for the past century has been an analysis of the similarities and differences between human milk and cow's milk. This contribution represents another item to be added to our knowledge of this subject. The paper describes the identification, occurrence, and some of the properties of a factor found in human milk in very much higher concentration than in cow's milk. The factor augments the growth of a particular mutant strain of *Lactobacillus bifidus*. The isolation of this factor is the result of an endeavor to explain the difference in the bacterial flora produced by human milk as compared with that occurring in infants fed cow's milk formulae. The colostrum and milk of a variety of species were tested for the concentrations of this growth factor, and data are included in this regard. The microbiological growth factor, was shown to be different from all known vitamins and growth factors. Various sources of this growth factor were sought and it was found that there was very slight activity in liver and none in yeast or meat. Meconium exhibited very high activity. Other sources of high activity were human semen, uterine mucus, gastric juice, saliva, amniotic fluid, and tears. It was particularly interesting to find that blood group substances A and B were highly active in this growth factor. Some preliminary information concerning the chemical composition of the growth factor obtained from human milk is provided. It would appear to be a nitrogen-containing polysaccharide possibly related chemically to the blood group substances. Certain far-reaching implications of this substance are discussed in relation to infection and malignancy. While this is certainly a most interesting growth factor, it must be remembered that thus far its role in human nutrition has not been established. It is a growth factor for a particular strain of *Lactobacillus bifidus* isolated from the stools. Further progress in this research will be awaited with great eagerness.—C. D. MAY

A survey—from the socio-economic standpoint—of the maternal factors influencing breast feeding is the subject of the following report.

Breast-Feeding in the Oxford Child Health Survey. Part I: A Study of Maternal Factors. C. Westropp. *Brit. Med. J.* 1: 138, 1953.

The paper reports a study of 574 mothers who attended the Oxford Child Health Survey. Women who breast-fed their babies for four months or more comprised 53.8 per cent of the sample, while 16.2 per cent breast-fed their babies for less than three weeks. The incidence of breast feeding in social classes I and

II was 66 per cent, in class III 54 per cent, and in IV and V 44 per cent. Classification with regard to favorable surroundings for childbearing divided the group into favorably situated, moderately situated, and poorly situated. The corresponding percentages of prolonged breast feeding were 64, 54, and 43. It was further found that if the social conditions are good, the incidence of prolonged breast feeding increases with increasing family size.—H. L. TAYLOR

The effect of breast milk upon the fecal flora and the occurrence of gastroenteritis in infants are subjects which require careful study. In the following paper, no decisive opinion is reached, although it is suggested that breast milk may decrease the incidence of certain types of E. coli *commonly associated with gastroenteritis.*

Infection and Nutrition in Diarrhoea and Vomiting of Infancy. C. A. C. Ross. *Glasgow M. J.* 33: 441, 1952.

Accumulating evidence indicates a relationship between certain serological types of *E. coli* (different types assuming epidemic importance at different places and times) and the eventual development of diarrhea and vomiting in infants. The author's observations in a series of 118 infants in a gastrointestinal ward were confirmatory of this relationship. Admission feces examinations showed *E. coli* types 0 111 or 0 55 to be present in 35.6 per cent of these infants, with the 0 111 type predominating. The presence of these organisms was more closely associated with moderate and severe gastrointestinal symptoms than with milder cases. Cross-infection resulted in the acquisition of one of these two types by 36.6 per cent of those infants whose feces were free of both types on admission. Follow-up studies were done on 25 of them, and 23 of these subsequently developed diarrhea, vomiting, or both.

Since gastroenteritis in infancy is primarily a disease of bottle-fed babies, an analysis was made of the feeding history of these infants, in an attempt to discover whether breast milk conferred immunity to these serological types and whether (as in the case of bovine colostrum, which procures lasting immunity from diarrheal disease in calves) such protection was permanent or limited to the period of breast feeding. It was found that 6 of 22 infants with moderate to severe gastroenteritis had been partially or completely breast-fed, as compared to 14 of 70 with mild symptoms. These differences are certainly not statistically significant. However, the author feels that further study, in a larger series, of the correlation between duration of previous breast feeding and severity of gastrointestinal symptoms is warranted. She believes that human milk should be investigated for its possible immunological properties against these types of *E. coli*.—C.-J. HOWELL

BREAKFAST

Nutritionists have become aware of the difficulties which occur in maintaining a normal dietary intake because of the propensity of many individuals to omit breakfast. There have been many studies in industry and among student groups designed to test the effect of an inadequate breakfast upon physical and mental efficiency. Having demonstrated a deleterious effect upon efficiency arising from the custom of a light breakfast snack, studies have been conducted to determine what type of breakfast, from the standpoint of caloric and protein intake, will promote increased efficiency.

Physiologic Response to Size and Content of Breakfast by Men Over 60. W. W. Tuttle, K. Daum, H. Roberts, and B. Randall. *J. Am. Dietet. A.* 29: 34, 1953.

Seven men, 60–84 years of age, served as subjects in a study of the relative effectiveness of various types of breakfasts in promoting efficiency in the late morning hours. Most of the men suffered from some of the common infirmities of men of their age but were able to cooperate without jeopardizing their health status. The subjects ate all meals in the hospital dining room. In a preliminary period of four weeks, while they were allowed free choice of foods—carefully recorded by the dietitian, none selected a diet best suited to his requirement. One, who was used to milk, crackers, and canned baked beans, avoided vegetables and desserts in favor of meat, potatoes, and gravy. Those who ate in restaurants favored fried foods. However, when the dietary for the experimental period was finally devised, few items were ever rejected from dislike or digestive disturbances. The authors believe that men this age are eager and capable of eating an adequate diet if they are properly motivated and if it is made available.

During three experimental periods of five weeks each, the subjects ate a basic cereal and milk breakfast, then a basic bacon-egg-milk breakfast and, finally, a heavy breakfast (which furnished 40 per cent of the protein and calories for 24 hours). During each period, physiologic tests were performed. These included (a) choice reaction time, (b) neuromuscular tremor magnitude, (c) maximum grip strength and grip-strength endurance, and (d) oxygen used to do a specified amount of work. Mean physiologic responses for each subject were compared during the three periods.

There was no differentiation in choice reaction time. neuromuscular tremor magnitude, maximum grip strength, grip-strength endurance, or oxygen required to perform a specified amount of work following the basic cereal-and-milk breakfast or the basic bacon-egg-and-milk breakfast. In ten of 14 comparisons, the subjects had a significantly shorter choice reac-

tion time following one or the other of the basic breakfasts than after the heavy breakfast. In 12 of 14 comparisons the grip strength endurance was greater after the basic breakfasts than after the heavy breakfast.

The authors conclude that a basic cereal and milk breakfast and a basic bacon-egg-milk breakfast of equal protein and caloric value (25 per cent of daily need) are equally effective in promoting mental and physical efficiency in the late morning hours. These are better than a heavy breakfast (40 per cent of daily protein and calories) in promoting mental and physical efficiency in late morning hours.—J. SMITH

The maintenance of the blood sugar for 3 to 3½ hours following breakfast by means of protein included at this meal is important in preventing the reactive hypoglycemia which may occur following a carbohydrate feeding. The actual source of protein appears to be unimportant, mixed plant and animal sources being as effective as those derived wholly from one or the other.

Effect of Protein Source on Maintaining Blood Sugar Levels after Breakfast. M. C. Coleman, W. W. Tuttle, and K. Daum. *J. Am. Dietet. A.* 29: 239, 1953.

There are several accounts in the literature which report that the *amount* of protein in the morning meal is important in maintaining the blood sugar above the fasting level for 3 to 3½ hours after breakfast.

The authors of this paper seek to answer the question as to what extent the protein *source* is important in maintenance of blood sugar level after breakfast. Bryant *et al.* have reported a study in which blood sugar levels of ten subjects were compared following two types of breakfast—one with protein chiefly of animal origin, the other chiefly of plant origin. It was concluded that the source of protein was unimportant in the maintenance of the blood sugar level following the breakfasts studied.

The paper herein reviewed reports blood sugar levels following consumption of breakfasts with almost all the protein of animal origin (95 per cent), and following breakfasts of similar proximate composition with practically all the protein of plant origin. Thirteen normal subjects, 8 males and 5 females, 16 to 27 years of age contributed fasting blood samples and samples at 30-minute intervals for 3½ hours after consuming the two types of breakfast.

It was found by comparisons of blood sugar levels that the breakfast in which the protein was 95 per cent of animal origin was as effective in maintaining the blood sugar above the fasting level as the breakfast in which plant protein was used. For 3½ hours after consumption of both breakfasts the blood sugar had not returned to the fasting level, though it had decreased markedly.

Published data for blood sugar increments of subjects eating breakfasts containing mixed proteins were compared with similar data in the present paper. Results were so much in agreement that the authors conclude that the consumption of breakfasts in which the protein is derived from both animal and plant sources is as effective in elevating and maintaining the blood sugar above the fasting level as is the consumption of a breakfast in which the protein is almost wholly of either plant or animal origin.—J. SMITH

The amount of protein required for maintenance of the blood sugar appears to be a minimum of 15 Gm. However, 25 Gm. of protein are recommended for the prevention of a postprandial decline of blood sugar levels.

Effect of Amount and Type of Protein in Breakfasts on Blood Sugar Levels. V. E. Addison, W. W. Tuttle, K. Daum, and R. Larsen. *J. Am. Dietet. A.* 29: 674, 1953.

Previous investigators have reported on the effectiveness of protein at breakfast in postponing declining blood sugar values. Conway compared blood sugar levels of college women consuming breakfast with 67 Gm. carbohydrate, 5 Gm. protein, 407 calories, or breakfasts with 34 Gm. carbohydrate, 25 Gm. protein, and 362 calories. The low protein was followed with a hypoglycemic lag between the second and third hours, and more constant blood sugar level was maintained after the higher amount of protein. Orent-Keiles *et al.*, using six or seven adult women, studied the effect on blood sugar of eight different food combinations for breakfast. The meals ranged from no food value to those providing 25 Gm. protein and more than 750 calories. After the higher protein, postprandial rise in blood sugar was normal, but the average maximal figure was lower, and return to fasting level was slower than after low protein breakfasts. Bryant *et al.*, in a similar study with men of two age groups, found 10 Gm. protein insufficient to hold blood sugar at or above fasting level for 3½ hours, but 25 Gm. protein was sufficient. Later Coleman *et al.*, using breakfasts with 25 Gm. protein and 770 calories, found plant protein as efficient as animal protein in maintaining blood level of 13 normal adults.

The present study attempted to answer the question as to whether 15 Gm. protein would maintain the blood sugar above the fasting level in the late morning hours; also, whether the source of the protein was important in maintaining blood sugar. Data were collected from 14 normal women 20 to 37 years of age. One menu, comprising apple juice, egg, cocoa, and jelly, supplied 517 calories. The other, of apricot, cereal, toast, peanut butter, and banana, contained 520 calories. Both supplied 15.0 Gm. protein.

On the basis of data presented it was concluded that although 15.0 Gm. protein in the breakfast was not sufficient to maintain blood sugar at or above the

fasting level for 3½ hours, the fall below the fasting level was not significant at any sampling period (repeated at 30-minute intervals). The data suggest that 15 Gm. protein is on the borderline with respect to maintaining the blood sugar at or above the fasting level for 3½ hours after the meal. Whether the protein is of plant or animal origin seems to be of no consequence, since the blood sugar behaved very similarly after the two breakfasts.—J. SMITH

According to dietary surveys in adolescent boys and girls, the recommended dietary allowances were achieved in those who consumed breakfast each day. It is probable that the failure of many parents to provide adequate breakfasts for school children contributes to the failure of many of these to achieve an adequate dietary intake of nutrients.

Role of Breakfast and of Between-Meal Foods in Adolescents' Nutrient Intake. B. F. Steele, M. M. Clayton, and R. E. Tucker. *J. Am. Dietet. A.* 28: 1054, 1952.

According to seven-day dietary records, 181 adolescent girls and 135 adolescent boys in Maine, New York, and Rhode Island ate breakfasts which contributed approximately one-fifth of the daily nutrient intake. Fifty per cent or more received less than one-fourth of their daily intakes of calories and of protein at breakfast. Boys and girls who always had breakfast more nearly met the recommended allowances for their age groups than those who missed breakfast once a week or more.

Between-meal foods contributed 10 per cent or less to the daily nutrient intake for the junior high school children from Maine and New York, but made substantial contributions to the intakes of calories, protein, calcium, and phosphorus of Rhode Island high school children.

Comparison of dietary adequacy was made between children who always ate breakfast and those who missed breakfast at least once a week. Data were grouped by states and for boys and girls. Eighty-eight per cent of the boys from New York, 87 per cent from Rhode Island, and 97 per cent from Maine ate breakfast every day. Similar data for the girls were 86 per cent in New York, Rhode Island 80 per cent, and Maine 96 per cent. The breakfasts of the boys contributed more to their daily intake and to their ability to meet the recommended allowances than did the breakfasts of the girls.—J. SMITH

VITAMIN A

The principal action of vitamin A is that of maintaining the mechanism within the retina responsible for visual acuity in dim light. In addition, this substance is important in the maintenance of the normal integrity of certain epithelial structures. Thus, the determination of adequate vitamin A nutrition may be made by testing dark adaptation time and by detection of changes in the conjunctiva. Few surveys have appeared dealing with the general aspects of vitamin A nutrition in the population.

Nutritional Status of Ten Family Groups in Washington State. II. Vitamin A Nutrition. L. W. Hardie and N. C. Esselbaugh. *J. Am. Dietet. A.* 29: 134, 1953.

The vitamin A nutriture of ten families at the beginning and end of a one-year period was determined by (1) records of dietary intake, (2) vitamin A and carotene blood serum determinations, (3) dark adaptation, and (4) degree of xerosis of the conjunctiva. Six of these families received extensive nutritional education. Four families served as controls.

Initial seven-day dietary records revealed that, in the main, the experimental group and all but one of the control families reported vitamin A intakes equal to or above the National Research Council allowances. The latter family showed improvement at the end of the year. Thus most of the people had adequate vitamin A intakes. The serum vitamin A and carotene levels of blood serum of all subjects were within "normal" limits. Dark adaptation, measured by the biophotometer according to the Jeans method, was poor initially as well as finally. The authors discuss the possibility that factors other than vitamin A nutrition may have affected the dark adaptation values.

Conjunctival xerosis, as measured by the biomicroscope, was not severe in either group, according to the authors. There is no statement concerning apparent differences in initial and final values for xerosis, though casual examination of the data suggests deterioration for both groups during the year (24 of 48 had lower scores and only 5 showed improved readings at the end).

The authors conclude that the vitamin A nutriture of the ten families may be described as average or above when determined by three of the four tests used in the study. Thus, because of the high initial intake, the educational program showed little effect of increased vitamin A intakes.—J. SMITH

The distribution of vitamin A within the body involves chiefly its storage within the liver. The precise location of vitamin A derivatives within the hepatic cells is the subject of the following observation.

Intracellular Distribution of Vitamin A Ester and Vitamin A Alcohol in Rat Liver. N. I. Krinsky and J. Gangully. *J. Biol. Chem.* 202: 227, 1953.

Though it is known that vitamin A is stored primarily in the liver, available information regarding the intracellular location of vitamin A is not conclusive. Using a technique of differential centrifugation, the author studied the relative distribution of vitamin A ester and vitamin A alcohol in the various cell fractions of rat liver homogenates. Vitamin A

ester was found to be concentrated in "the centripetally migrating material." Vitamin A alcohol was also present in this fraction, as well as in the supernatant and microsomal fractions. There was little vitamin A in the mitochondrial and nuclear fraction. As a consequence of these observations, the authors suggest that the vitamin A ester and vitamin A alcohol are associated with different proteins during storage within the liver cells.—M. K. HORWITT

Experimental animals maintained on a vitamin A-deficient diet are shown to manifest alterations in the rate of osteogenic processes. Neurologic manifestations of vitamin A deficiency may be related to changes in the growth rate of the skeleton and central nervous system.

Vitamin A Deficiency in the Duck. Skeletal Growth and the Central Nervous System. S. B. Wolbach and D. M. Hegsted. *Arch. Path.* 54: 548, 1952.

The dependency of certain neurologic signs and neuropathologic findings in the young chick and several species of mammals deficient in vitamin A upon primary changes in the axial skeleton was established by Wolbach almost two decades ago. Since Fletcher and Rigdon have recently asserted a direct and primary effect of vitamin A deficiency on the nervous system of young ducks, it may not be remiss to summarize Wolbach and Hegsted's recent findings and conclusions:

1. Changes in the vitamin A-deficient young duck are precisely similar to changes in other species previously studied.

2. A deficiency in young ducks results in prompt retardation and suppression of epiphyseal cartilage cell sequences concerned in endochondral bone growth, and therefore a disproportionate growth of the axial skeleton and central nervous system adequate to account wholly for all consequent neurologic manifestations.—J. GRUHN

Hypervitaminosis A has been responsible for the appearance of skeletal changes and other clinical abnormalities in the human infant.

Here, the effects in an adult of massive doses of this vitamin are reported.

Vitamin A Intoxication, Report of a Case in an Adult. E. Bifulco. *N. Eng. J. Med.* 248: 690, 1953.

Until recently, vitamin A intoxication had been reported only in infants and children, though it is not necessarily limited to this age group. The major clinical symptoms of the syndrome appear to be the same whether it occurs in adults or children. The case reported here describes the clinical symptoms in a 52-year-old woman.

This patient had been taking 100,000 I.U. of vitamin A daily under a physician's direction to cure a skin condition. After a year of this regime she began to suffer from insomnia and restlessness. A loss of hair from eyebrows, eyelashes, axillary and pubic areas was noticed several months later, accompanied by stiffness and pain in the joints. There was a progressive loss of appetite and weight. A month before the vitamin therapy was ended the patient complained of a pulsating headache and noted oozing of blood from the nose and mucous membranes of the eye and ear. Six months after the vitamin therapy had been discontinued, symptoms of the hypervitaminosis disappeared; the joint pains subsided, hair started to grow, appetite improved, and bleeding from the mucous membranes ended.

This report suggests that physicians administering large doses of vitamin A should be on the lookout for signs and symptoms of vitamin A intoxication.—M. W. BATES

The following papers deal with the influence of excessive vitamin A in experimental situations. Specific pathological changes in bone formation, development of congenital abnormalities and alterations in tissue cultures have all been noted. Although these reports deal with highly specialized experimental situations, the fact that excessive amounts of a vitamin can produce significant modifications of tissue structure opens new fields of study.

Hypervitaminosis A in Young Ducks. The Epiphyseal Cartilages. S. B. Wolbach and D. M. Hegsted. *Arch. Path.* 55: 47, 1953.

This article is the final one of a series demonstrating that the skeletal response of the young duck to vitamin A is similar to that which occurs in the chick and several other mammalian species. Here is a concise description and a clear-cut photographic demonstration of the histopathology of hypervitaminosis A in the bones of the knee, femur, tibiotarsus, vertebrae, and mandible—with emphasis on epiphyseal cartilage sequences concerned in advancing endochondral bone growth and the resorption of bone and compact bone formations at sites of remodeling.

The outstanding features of the epiphyseal cartilage of long bones in the hypervitaminosis duck were a narrow zone of proliferating cells, a relatively wide zone of growing cells, no clear demarcation between zones of proliferation and growth, and a very narrow zone of maturing and matured cells which was deeply penetrated by the tunnels characteristic of endochondral bone growth in birds. In essence, endochondral ossification was accelerated in the duck as in the other species previously studied. Similar but less evident acceleration was manifested in the axial skeleton. Cortical bone showed less increase in density (compact bone formation) than similar specimens from chicks.

Wolbach repeats his conviction that vitamin A has properties like those of inductor or evocator agents and suggests that the recent work of Fell and Mellanby almost compels the conclusion that vitamin A acts directly upon component cells.—J. GRUHN

Excessive Intake of Vitamin A as a Cause of Congenital Anomalies in the Rat. S. Q. Cohlan. *Science* 117: 535, 1953.

Congenital anomalies can be produced by an alteration in the chemical, endocrine, mechanical, and actinic environment of the fetus. Defective offspring have also been produced by deficiencies in the maternal diet of single nutrients, such as copper, iodine, riboflavin, pantothenic acid, folic acid, and vitamin A. In this study, very large doses of vitamin A were administered to pregnant rats by stomach tube. This resulted in a marked reduction in the number of litters carried to term. There was a successful pregnancy rate of 88 per cent in the 50 control animals, but only 10 per cent in the 100 experimental animals. Congenital cranial anomalies occurred in 54 per cent; no anomalies were noted in 410 offspring of the control group. Other anomalies noted sporadically were harelip, cleft palate, macroglossia, and defects in eye development. It is interesting that the cranial deformity was comparable to that produced in mice by hypoxia. —S. O. WAIFE

Metaplasis Produced in Cultures of Chick Ectoderm by High Vitamin A. H. B. Fell and E. Mellanby. *J. Physiol.* 119: 470, 1953.

High vitamin A completely suppressed keratinization of 6–7 day explants of chick embryonic ectoderm. The ectoderm differentiated into mucus-secreting epithelia which was often ciliated. This resembled normal nasal mucosa. Control explants in normal media formed keratinizing squamous epithelium. When transferred from high vitamin A to normal media differentiation was accelerated at first and reached an advanced stage. However, under these conditions, the basal cells began to differentiate into squamous keratinizing epithelium instead of secretory cells. The keratinizing epithelium formed beneath the secretory layer. Later, the ciliated and secretory cells were shed.—M. J. OPPENHEIMER

Since vitamin A is a fat-soluble vitamin, its absorption is indicative of fat absorption generally. This principle was used in a clinical test and in a study of gastrectomized subjects.

Observations on the Vitamin A Tolerance Curve as an Index of the Degree of Fat Absorption. C. W. Legerton, Jr., E. C. Texter, Jr., and J. M. Ruffin. *Gastroenterology* 23: 477, 1953.

The authors performed fat balance and vitamin A absorption studies on 28 patients including normal subjects and patients with various gastrointestinal diseases. Results indicate that the absorption of vitamin A from an oily vehicle as measured by the plasma vitamin A level at the end of 5 hours is a fairly reliable index of the ability of the body to absorb fat. Such a test could not be used in the presence of liver disease.—S. H. LORBER

Disturbances of Vitamin A Absorption and Their Permanency in Gastrectomized Subjects. H. Gounelle, H. Teulon, C. Marnay, and G. Martinez. *Bull. Acad. nat. méd.* 136: 554, 1952.

In order to study disturbances of vitamin metabolism in the gastrectomized subject, the authors carried out hypervitaminemia A tests in 3 groups of patients.

In 7 subjects who had undergone a recent gastrectomy (9 to 28 days previously) the test revealed the complete absence of the hypervitaminemia response.

In 6 patients who had been gastrectomized earlier (4 to 10 years previously), 10 tests were equally negative, even with Tween®. This demonstrates that the disturbance of vitamin absorption persists in gastrectomized patients.

In the course of the same test 3 controls showed a positive vitaminemia response. One patient with hyperchlorhydric gastritis also showed this reaction. On the other hand, three subjects with cancer of the stomach before operation had only a slightly elevated response. The authors stress this disturbance of nutrition in the patient with gastric neoplasm.

In conclusion, the authors recommend extensive vitamin therapy in all gastrectomized patients, whether the operation was recent or not.—H. GOUNELLE

FURTHER STUDIES ON CHOLESTEROL

The absorption of dietary cholesterol and presumably of cholesterol produced endogenously may be markedly retarded by the feeding of certain plant sterols or other cholesterol derivatives. This finding presents the possibility of the therapeutic application of these substances in the treatment of disorders involving cholesterol metabolism and deposition in the blood vessels.

Prevention of Plasma Cholesterol Elevation and Atheromatosis in the Cholesterol-Fed Bird by the Administration of Dihydrocholesterol. M. D. Siperstein, C. W. Nichols, Jr., and I. L. Chaikoff. *Circulation* 7: 37, 1953.

Chicks fed 2 per cent dihydrocholesterol plus 1 per cent cholesterol fail to develop the hypercholesterolemia, hyperlipemia and atherosclerosis induced by a diet of 1 per cent cholesterol alone.—J. STAMLER

The absorption of cholesterol-lipid complexes from the gastrointestinal tract is facilitated by the presence of bile. The removal of bile salts by precipitation with ferric ion appears to be an effective means of preventing cholesterol absorption.

Effects of Ferric Chloride and Bile on Plasma Cholesterol and Atherosclerosis in the Cholesterol-fed-Bird. M. D. Siperstein, C. W. Nichols, Jr., and I. L. Chaikoff. *Science* 117: 386, 1953.

The absorption of cholesterol from the intestinal tract requires the presence of bile. Since ferric chloride can precipitate bile salts *in vitro*, it was interesting to study whether the rise in plasma cholesterol, as well as the associated atheromata resulting from cholesterol feeding, could be prevented to a large degree by the feeding of ferric chloride.

It was demonstrated that the feeding of iron, even in the presence of bile, held plaque formation to a degree approximately one-fifth that observed in birds fed cholesterol alone. Feeding ox bile along with cholesterol resulted in a greater degree of atherosclerosis and hypercholesterolemia than that following the feeding of cholesterol alone. Thus it would appear that the oral administration of ferric chloride reduced the rise of plasma cholesterol in birds fed cholesterol, as well as in those fed cholesterol plus bile. It is probable that iron acts by precipitating bile salts in the intestinal tract.—S. O. WAIFE

The following studies involve the effects of various substances and diets upon the absorption of cholesterol. The importance of fatty acids is demonstrated in rats, and that of total fat in international studies.

Factors Influencing Cholesterol Absorption. K. S. Kim and A. C. Ivy. *Am. J. Physiol.* 171: 302, 1952.

Using the difference between dietary and fecal sterol levels as a criterion, it was demonstrated that fat in adequate amounts facilitates the absorption of cholesterol. The fatty acid portion of the fat molecule is responsible for this facilitation. Oleic acid was more effective than corn oil in promoting absorption of simultaneously administered cholesterol. Cholic acid increased serum cholesterol levels in rats given oleic acid and cholesterol, but not in significant amounts when corn oil and cholesterol were used. Diet influenced fecal phospholipid excretion. On fat-free diets only traces of fecal phospholipid were found, and these were not increased by the addition of cholesterol or glycerol to the diet. However, when corn oil and free fatty acids were added, then fecal phospholipid excretion was increased. Serum cholesterol was elevated by thiouracil even when the diet contained no fat or cholesterol. Weight loss due to thyroid feeding was diminished by corn oil but not by cholesterol.—M. J. OPPENHEIMER

Atherosclerosis: A Problem in Newer Public Health. A. Keys. *J. Mt. Sinai Hosp.* 20: 118, 1953.

Experiments with cholesterol in man reveal that about 20 to 50 per cent of cholesterol ingested in a fat vehicle is absorbed from the gut. Following the administration of large amounts of cholesterol in a fat-rich meal, the maximum rise in blood level occurred several hours later, the value at 4 hours often being the peak.

In 73 healthy men a breakfast of toast, butter, scrambled eggs, and coffee with cream plus 10 Gm. of cholesterol resulted in a mean serum rise of about 4 mg. per 100 ml.—or less than 3 per cent of the total ingested cholesterol. In about 24 hours the serum level no longer showed any trace of this single massive dose.

While there are many observations on the effects of acute or short-term changes in cholesterol and/or fat intake, homeostatic forces seem to cause a reversion to the original pattern. Hence, a survey of population groups that habitually ingested different diets was made. Summarizing the extensive information in this report, it should be noted that a close correlation was found between the proportion of total calories derived from fat and the deaths from "degenerative" heart diseases in Japan, Italy, England, Australia, Canada, and the U.S.A. The last-named country led in cardiovascular deaths and in the level of fat in the diet. According to Keys, the key to the clinical problem of atherosclerosis lies in the relative and absolute amounts of fat in the diet; if so, this is truly a public health problem of paramount importance.—S. O. WAIFE

It is interesting to note that when considered from the standpoint of the caloric contribution to the diet, meat and milk sources are comparatively low in cholesterol content. It is suggested that the level of caloric intake may be more important in atherogenesis than the level of cholesterol consumption.

Cholesterol Studies. I. The Cholesterol Content of Foods. A. Piehl. *Scand. J. Clin. Lab. Investig.* 4: 115, 1952.

An analysis of the cholesterol content of food obtained in Oslo, Norway, was made. Attention is called to the fact that lean meat, fish, and fish products are important cholesterol sources. The author believes that too much attention has been placed on milk and animal fat as sources of cholesterol. He further states that when cholesterol-containing foods are compared on a caloric basis, animal fat and milk are low in cholesterol content. If a truly low cholesterol diet is desired, animal products must be almost excluded.—S. O. WAIFE

Cholesterol Studies. II. Dietary Cholesterol and Atherosclerosis. A. Piehl. *Scand. J. Clin. Lab. Investig.* 4: 122, 1952.

A correlation study was made of the mortality rate from cardiovascular diseases in Norway during the Second World War, with concurrent dietary changes. It was found that the consumption of cholesterol was reduced from more than 500 mg. per person per day in prewar years, to 300 to 400 mg. per day during the war years. The finding that the cholesterol intake was only moderately reduced in spite of a strongly decreased consumption of such cholesterol-containing products as eggs, meat, meat products, milk, cream, and cheese is explained by the author as follows:

During World War II, significant quantities of cholesterol were supplied by the increased consump-

tion of fish, fish products, and cod-liver oil. Furthermore, margarine, which contained higher proportions of cholesterol-rich herring oil, was used. The author does not believe, therefore, that the reduced cholesterol intake during the war years can account for the observed reduction in mortality rate due to cardiovascular diseases; and it may be that the level of fat and caloric intake may be more important in atherosclerosis than the level of cholesterol consumption.—S. O. WAIFE

The authors of the following paper employed choline, inositol, and a dispersing agent, polysorbate 80, as a means of reducing serum cholesterol in hypercholesterolemic patients. Although it is stated that lipotropic agents are essential in fat transportation, there is no indication that an inadequacy of these substances existed in these patients. The average diet apparently supplies an adequate intake. The action of dispersing agents in cholesterol transport and utilization has not been shown to exert a favorable effect under experimental conditions. One must be cautious in recommending treatment with this material until further knowledge has accumulated.

Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex. D. A. Sherber and M. M. Levites. *J. A. M. A.* 152: 682, 1953.

Sixteen patients with serum cholesterol levels above 306 mg. per 100 cc. were given daily 20 cc. of a solution containing a "complex" of polysorbate 80, and choline and inositol in divided doses. In 15 of the 16 subjects there was a significant drop in serum cholesterol levels, associated with a rise in the output of urinary cholesterol. Furthermore, there was a rise in the formaldehydogenic steroids but no change in 17-ketosteroids in the urine. These changes were not found in a patient with Addison's disease and hypercholesteremia.

It is interesting that a survey of 960 consecutive patients revealed that 13.7 per cent had a serum cholesterol value of 300 mg. per 100 cc. or over. About two-thirds of the hypercholesteremic patients had cardiovascular disease and one-fifth had diabetes.

Polysorbate 80 is an effective dispersing agent. Choline and inositol are also essential in the formation of substances necessary for fat transport. The authors believe that, in view of the fact that the preparation produces no apparent change in the serum or urinary levels of cholesterol and corticoids in persons with normal cholesterol levels, in hypercholesteremic patients, at least, the state of serum cholesterol "is such as to hinder its utilization by the adrenal cortex." The use of this material seems to "alter the state of serum cholesterol to make the cholesterol molecule more easily filterable through the renal glomerulus and more accessible to the adrenal cortex for its requirements."

As the authors rightly point out, the number of patients and the length of the study are too limited for sweeping conclusions.—S. O. WAIFE

The endogenous synthesis of cholesterol by the liver has been shown to be sharply enhanced during periods of dietary restriction of this substance, so that cholesterogenesis may be regulated by a homeostatic mechanism, and dietary restriction may be of no importance in the control of arteriosclerosis. However, as mentioned previously, methods may be available for the prevention of the absorption of endogenously formed cholesterol.

Cholesterol Synthesis by Liver. III. Its Regulation by Ingested Cholesterol. G. M. Tomkins, H. Sheppard, and I. L. Chaikoff. *J. Biol. Chem.* 201: 137, 1953.

It has repeatedly been shown that in some individuals the cholesterol concentration in blood remains constant for long periods of time in the postabsorptive state. Since the liver is the most likely site for the synthesis of plasma cholesterol, the question as to whether cholesterogenesis in the liver is under homeostatic control was investigated.

Liver slices prepared from rats fed diets containing 5, 0.5, and 0 per cent cholesterol were incubated with C^{14}-acetate and the incorporation of C^{14} into cholesterol was determined. When the diet containing 5 per cent cholesterol was fed for eight days the cholesterol synthesis from acetate in the liver practically stopped. A marked depression in synthesis was observed in livers of rats fed the 0.5 per cent cholesterol diet for seven days. Thus it is clear that a mechanism exists for the control of cholesterol synthesis in the liver.

There seems to be little doubt that the ingestion of enormous amounts of cholesterol is deleterious to the cardiovascular system. Because of this, severe restriction of the cholesterol in the diet has been advocated. However, it has been shown that the liver of a rat fed a diet entirely devoid of cholesterol for eight days has a much greater capacity for cholesterogenesis than does the liver of a rat fed a 0.5 per cent cholesterol diet. The authors raise the question as to whether severe restriction of dietary cholesterol offers any real advantage in the control of arteriosclerosis.—M. K. HORWITT

An interesting study on the synthesis of cholesterol by the chick embryo indicates that labelled acetate is converted to cholesterol in the embryo proper.

Metabolism of Cholesterol in the Chick Embryo. I. The Synthesis of Cholesterol. W. M. Stokes, W. A. Fish, and F. C. Hickey. *J. Biol. Chem.* 200: 683, 1953.

Sodium acetate, labeled in the carboxyl group with C^{14}, was injected into Rhode Island Red eggs which were examined after varying periods of incubation. The eggs were divided into four portions: embryo, yolk sac, other embryonic membranes, and the remainder, including the yolk. The results indicated

that injected carboxyl-labeled sodium acetate is continuously incorporated into the cholesterol of the fertile hen's egg during the latter half of incubation. While the largest percentage of conversion occurred in the embryo proper, the specific activity of the cholesterol of the membranes was always much greater than that of the embryo. Toward the close of incubation, a shift of activity occurs from all the embryonic membranes to the embryo.—M. K. HORWITT

The importance of the liver as the site of removal of cholesterol from the blood and conversion of this substance into bile acids has been demonstrated.

Observations Concerning Production and Excretion of Cholesterol in Mammals. VIII. Fate of Injected Cholesterol in the Animal Body. M. Friedman, S. O. Byers, and B. Gunning. *Am. J. Physiol.* 172: 309, 1953.

In these experiments it was demonstrated that the liver was chiefly responsible for removal of excess cholesterol from the blood. This increased amount of cholesterol was provided by injecting hypercholesteremic rat serum into recipient rats. In the recipients the hypercholesteremia so induced disappeared in 12 to 24 hours. Some evidence was presented to the fact that at least 60 per cent of injected cholesterol was converted and excreted as bile acid.—M. J. OPPENHEIMER

In hyperthyroidism, the blood cholesterol is generally found to be reduced. Contrariwise, hypothyroidism is associated with elevation of the blood cholesterol. The following work suggests that there is an increased rate of synthesis and destruction of cholesterol in hyperthyroidism, and that the opposite effects are observed in hypothyroidism.

The Mechanism Responsible for the Altered Blood Cholesterol Content in Deranged Thyroid States. R. H. Rosenman, S. O. Byers, and M. Friedman. *J. Clin. Endocrinol.* 12: 1287, 1952.

That blood cholesterol levels are altered in both hypo- and hyperthyroid states is well known. Rosenman, Byers, and Friedman studied the metabolism of radioactive cholesterol in rats with induced hyper- and hypothyroid states. The results of these investigations indicate that hyperthyroidism was associated with a markedly increased rate of hepatic synthesis, destruction, and intestinal excretion of cholesterol. The lower plasma cholesterol levels in hyperthyroidism are probably due to the difference in the degree of the change in synthesis and elimination of cholesterol. On the other hand, hepatic synthesis of cholesterol was greatly reduced in hypothyroidism, but there was an even greater decrease in the rates of destruction and intestinal excretion of cholesterol, so that there is a resultant hypercholesterolemia. In other words, there was a "disparity" between manufacture and elimination of cholesterol under various thyroid situations.—S. O. WAIFE

SOME ASPECTS OF CALCIUM METABOLISM

An interesting technique for the study of calcium metabolism in the human has been developed by the use of radiocalcium and ethylene diamine tetracetic acid. Because of the difficulty involved in metabolic balance studies and the uncertain interpretation of calcium infusion tests, the development of an indicator of bone metabolism is awaited with great interest.

Metabolism and Removal of Ca^{45} in man. J. Bellin and D. Laszlo. *Science* 117: 331, 1953.

The metabolism and removal of Ca^{45} in man was studied by the administration of a single tracer dose of high specific activity radiocalcium. Five minutes after the administration of $Ca^{45}Cl_2$ to a patient with multiple myeloma and primary hyperparathyroidism, 26 per cent of the dose of 57.6 μc. of Ca^{45} was found in the circulation; 4.3 per cent of the injected dose was present after 24 hours. The radiocalcium appeared rapidly in the urine: 0.64 per cent in 30 minutes, and 7.4 per cent after 24 hours. Feces contained 0.8 per cent of the dose during the first two days. Fourteen days after administration of the tracer dose a total of 40.4 per cent was accounted for: 0.9 per cent remained in the serum, 32.7 per cent excreted in the urine and 6.8 per cent in the stool. The patient died on the fourteenth day of an intercurrent fulminating pneumonitis. The Ca^{45} contained in the skeletal mass accounted for practically all of the calcium content remaining in the body.

The sodium salt of ethylene diamine tetracetic acid (EDTA) is a strong chelating agent which forms complexes with calcium and other metallic ions causing a marked excess calcinuria without lowering of serum calcium levels after intravenous administration to man. When 57.6 μc. Ca^{45} was administered to a patient with prostatic cancer and osteoblastic metastases relatively little Ca^{45} was excreted in the urine of this patient. Fifteen days after the administration of the isotope 4 Gm. Na-EDTA was infused for six hours on three successive days. This was followed by a tenfold increase in the excretion of both calcium and Ca^{45}, with maximum excretion noted during and shortly after the completion of the infusion. Twenty-four hours later excretions were only slightly above the pre-infusion levels.

The rate at which these processes take place may represent a more useful indicator of skeletal activity than the metabolic balance studies and the calcium-tolerance tests previously employed.—M. K. HORWITT

The diagnosis of demineralizing skeletal processes is not always easy. In the absence of any obvious causes of bone decalcification in the older age group, the diagnosis of osteoporosis is usually made. In the following study, low calcium intakes were associated with osteoporosis, and a causal relationship was

suggested. It is obviously difficult to establish the actual basis for skeletal demineralization at the present stage of our knowledge.

Calcium and Phosphorus Intake in Senile Osteoporosis. N. Vinther-Paulsen. *Geriatrics* 8: 76, 1953.

A survey of the calcium intake of 33 ambulatory patients (ages 68–96 years) revealed a marked individual variation. This ranged from 200 to 1100 mg. a day, in spite of the fact that none of the subjects was suffering from an acute disease with anorexia and that the supply of calcium in the form of milk and cheese was available *ad libitum*. Senile osteoporosis was found in three-fourths of the subjects habitually ingesting under 0.5 Gm. of calcium daily. It was noted in only 14 per cent of those with a higher calcium intake. Similarly, using 0.9 Gm. phosphorus as a dividing line, two-thirds of those taking less and one-tenth of those taking more than this showed osteoporosis. The serum levels were normal in all.

This does not prove, but suggests, that prolonged inadequate intake of Ca and P may predispose to the development of osteoporosis. It is also likely that a deficiency of other substances, particularly vitamin D and protein, may play a role.—S. O. Waife

The following study suggests, as have others, that the primary defect in osteoporosis is in the deposition of calcium salts in bone matrix, probably because of a reduction of calcifiable matrix.

Calcium, Phosphorus, Nitrogen, and Potassium Balance Studies in the Aged Male. M. D. Bogdonoff, N. W. Shock, and M. P. Nichols. *J. Gerontol.* 8: 272, 1953.

Calcium metabolism was studied in seven elderly male subjects by the balance technique. In the presence of a relatively high protein diet, approximately 850 mg. of calcium per day was adequate to effect calcium equilibrium. Furthermore, aged male individuals retained the ability to store nitrogen and phosphorus and potassium, and presumably thereby, to build protoplasm. It was also noted that aged male individuals with evidence of osteoporosis, who were concurrently storing nitrogen, did not greatly increase their calcium retention when large amounts of calcium were supplied. This suggests either a defect in the building of bone matrix or a defect in the ability to incorporate calcium salts into the protoplasmic matrix.

This level of calcium intake is not greater than the requirement for young adults, but increasing the calcium in the diet increased the daily retention.—S. O. Waife

Calcium and Phosphorus Balance in Elderly Men. P. G. Ackermann and G. Toro. *J. Gerontol.* 8: 289, 1953.

Although it is reported in literature that 8 to 12 mg./Kg./day of calcium are needed for young adults, balance studies in eight elderly men suggested that 18.5 mg. of calcium/Kg./day are necessary to maintain calcium balance. The phosphorus intake required for equilibrium was 18.7 mg./Kg./day. These authors conclude, unlike the report by Bogdonoff, Shock, and Nichols, that the calcium requirement is greater for old men than for young adults, although the phosphorus requirement seems to be in the same range of magnitude.—S. O. Waife

The influence of phosphate and other substances upon calcium balance has been widely studied. Recent investigations from several laboratories indicate that the level of calcium balance is not significantly influenced by wide variations in the level of concomitant phosphate feeding. Rather it is the level of calcium in the diet per se *which determines the calcium balance in the normal human.*

Phosphates and Phosphoric Acid as Dietary Factors in the Calcium Balance of Man. O. J. Malm. *Scand. J. Clin. Lab. Investig.* 5: 75, 1953.

There is conflicting evidence regarding the effect of phosphates on the absorption of calcium in man. This report is a detailed study of calcium and phosphorus balance over long periods of time in healthy human volunteers. The results may be summarized as follows:

Phosphorus (in the form of phosphoric acid) given daily for one week to adult men engaged in active work gave a slight decrease in urinary calcium in three cases, but a significant decrease in one. Larger doses of phosphorus also reduced urinary calcium output but calcium balance remained the same. This meant that somewhat more calcium was appearing in the stools. Similarly, raising the phosphorus level in the diet from 1.4 to 2 Gm. in two active adults had no effect on calcium balance over a period of twelve weeks, the calcium intake remaining constant. Further evidence shows that the majority of normal individuals on very low calcium intakes adapt themselves in about a week's time and show rather small variations in fecal calcium. The saturation of the body, or the daily need for calcium, plays a major role in determining the length of the adjustment period following such changes in calcium and/or phosphorus intake.—S. O. Waife

In the formation of bone, the action of phosphatase and phosphorylase has been under some dispute. In the following study, it is suggested that their chief effects are exerted through the production and orientation of the matrix glycoproteins.

Relation of Glycogen, Phosphorylase, and Ground Substance to Calcification of Bone. J. D. Cobb. *Arch. Pathol.* 55: 496, 1953.

Glycogen, glycogenolytic enzymes, and the ground substance are intricately involved in the process of bone calcification. Cobb begins with the supposition that phosphatase and phosphorylase may exert their chief effects in calcification through mobilization and

orientation of ground substance. For her study, the tibia of normally growing, rachitic, and healing rachitic rats were prepared by freezing-drying fixation and carnauba wax imbedding, which permits study of undecalcified bone. Glycogen and bone salts were removed and bone sections were incubated at appropriate pH with glucose-l-phosphate and BaCl. Under these circumstances, the identification of glycogen by the Hotchkiss stain served to localize the sites where phosphorylase occurs.

$$\text{glucose-l-phosphate} \underset{\text{phosphorylase}}{\rightleftharpoons} \text{glycogen} + \text{phosphate}$$

The BaCl is used to precipitate phosphate ions.

The bone and cartilage cells most consistently found to show phosphorylase activity are those that contained glycogen at some period in their development but are temporarily lacking in it. These cells occur in areas showing the most rapid formation of calcifiable matrix glycoproteins. The experimental findings consistently point to the conclusion that the consumption of glycogen through the activity of phosphorylase may possibly be associated with the production of bone matrix and rachitic osteoid and with the production or alteration of cartilage matrix prior to calcification. The precise relationship of cell glycogen and phosphorylase to the manufacture of bone constituents is obscure. At present, it is difficult to assign a definite role to the phosphatase and phosphorylase shown to be active in bone.—J. GRUHN

The clinical effects of disorders of calcium metabolism may be reflected in the roentgen appearance of the bones. The differential diagnosis of the "porous" bone is important.

Generalized Decreased Bone Density. D. M. Gould. *Am. J. Med. Sc.* 223: 961, 1952.

The radiologist is in a position to recognize and suggest the differential diagnosis of decreased bone density. The anatomy and physiology of normal bone are discussed in this paper. Two types of decreased bone density are recognized—malacic bone and osteoporotic bone. Malacic bone, which lacks calcium salts but has an adequate osteoid matrix, is softer, more flexible, more pliable, and generally lacks the rigidity associated with normal bone. Its causes are: (*A*) nutritional—(1) vitamin D lack—rickets, (2) mineral and vitamin D lack—osteomalacia, (3) vitamin D resistant—refractory rickets, (4) gastrointestinal tract disease—steatorrhea from various causes, and inadvertent gastro-ileostomy; (*B*) renal disease; (*C*) endocrine disease—hyperparathyroidism. Each of the above is discussed in detail and charts of roentgen and chemical differential diagnosis are appended.

Osteoporosis is associated with diseases primarily due to disturbance in the organic component. This phase is very poorly understood. Causes of osteoporosis are (1) congenital osteogenesis imperfecta; (2) lack of stress and strain (disuse atrophy); (3) endocrine—postmenopausal androgen lack, Cushing's syndrome, "alarm reaction," hyperthyroidism, hypothyroidism, acromegaly, Simmond's disease; (4) nutritional scurvy and malnutrition; (5) degenerative (senile osteoporosis); (6) unknown. For detailed discussion of the physiopathology of each of the above, the reader is referred to the original article. Numerous excellent tables have been included and the article constitutes an excellent review of the present knowledge of the subject of bone density as related to medical diagnosis.—G. T. WOHL

The influence of dietary calcium and phosphate upon dental caries is well established. Prevention of experimental caries in rats was achieved by the supplementation of the diet with rock phosphate.

Prevention of Dental Caries by Rock Phosphate in the Diet of the Rat. J. F. McClendon and J. Gershon-Cohen. *Science* 117: 595, 1953.

Rats were fed a special cariogenic diet which led to the development of caries in 61 per cent of the animals. When this diet was supplemented with 20 Gm. of rock phosphate, the incidence of caries fell to 21 per cent. On a diet supplemented with 34 Gm. of rock phosphate, the incidence fell to 5 per cent. The calcification of the entire skeleton was better in rats on the supplementary diet.

The rock phosphate material contains about 6 per cent of calcium fluoride, but is in a much more insoluble form than the usual sodium fluoride. Obviously, time and more work are needed before any of these results can be interpreted in the light of human dental caries.—S. O. WAIFE

The following case report may be of interest, but no explanation for the effect of calcium as observed in the treatment of abnormal bleeding can be hypothesized.

The Favorable Response of Atypical Hemophilia to Calcium. H. Kramer, W. N. Donovan, and M. F. Beard. *U. S. Armed Forces M. J.* 4: 761, 1953.

The authors report, without attempting to explain, a case in which calcium was successful in treating hemophilia in a patient whose blood calcium levels were normal.

The patient, a 24-year-old man, was first seen on account of bleeding persisting a week after a dental extraction. He gave a history of prolonged bleeding after dental manipulation, but claimed abnormal bleeding had not occurred after cuts and abrasions. Bleeding time on admission was 2 minutes, 25 seconds; clotting time, 10 seconds; prothrombin time, 13.3 seconds. Blood calcium on the day after admission was 10 mg. per 100 cc. Since a 4–5 day bleeding incident following an earlier dental treatment (1948) had responded to an oral calcium preparation, 10 cc. of 10 per cent calcium gluconate was given intravenously for several days, together with 1 Gm. of

oral calcium gluconate, 3 times a day. Bleeding stopped on the day after institution of treatment. A further extraction was performed while calcium was being administered, and no immediate bleeding resulted. Parenteral calcium was stopped after the first day after this second extraction, and all calcium was discontinued after the second day. On the third day, bleeding began at the site of the extraction, and on the fifth day 10 cc. of a 10 per cent solution of calcium was given intravenously. On the eighth day, the bleeding stopped, and calcium injections were discontinued. On the twelfth day, bleeding recurred, ceasing spontaneously after 2 days.

The authors feel the success attained with calcium in this case was not predictable from authoritative statements on the subject in the literature. Marked prolongation of coagulation time was to be expected only with a reduction of total calcium to 2.5 mg. per 100 cc.; but the hemorrhagic diathesis due to prothrombin deficiency and the clinical response to calcium which characterized this case suggest a diagnosis of *hemophilia calcipriva* despite the normal blood calcium levels.—C.-J. Howell

ITEMS OF GENERAL INTEREST

Potency of Vitamin Products. J. A. Campbell. *Canad. M. A. J.* 68: 103, 1953.

The author discusses factors affecting the potency of vitamin products and points out that there may be very marked differences between manufacturers and the reliability of their vitamin products. Hence, in the successful treatment of any nutritional disorder, two factors are necessary: the therapeutic agent must be present in the expected or labeled amount; it must be available to the patient.

Manufacturers are separated into two categories—those exercising control in their manufacturing, and those without control. It was found that only 2 out of 128, or about 1.5 per cent, of the controlled products tested were deficient; while 166 out of 313, or more than 50 per cent, of noncontrolled products did not meet the labeled requirements in one or more vitamins. The difference is particularly noticeable in the case of vitamin A, thiamine, pantothenic acid, and ascorbic acid, which is to be expected since these vitamins are more readily decomposed by improper conditions than the others. Deficiencies found are brought to the attention of the manufacturer, and it is pointed out that no report can be made to the profession regarding the deficiencies, for these matters are confidential. However, clinicians may be assured that any action required will be taken promptly and followed through until a better factory product is assured. An intensive campaign is well under way to have all vitamin products manufactured under proper analytical control; nevertheless, on account of their relatively low stability compared with many other pharmaceuticals, it is suggested that clinicians give serious thought to the selection and prescription of vitamin products.—G. C. Cochrane

A Mechanism of Regulation of Food Intake. J. L. Strominger and J. R. Brobeck. *Yale J. Biol. & Med.* 25: 383, 1953.

What an animal eats, or how much, is usually thought to be determined by the energy requirements of the body. However, there is no simple correlation between energy needs and food intake which is valid under all circumstances. In this paper, the authors present a hypothesis which basically states that the important factor in regulation of food intake is not the energy value of the food *per se*, but rather the amount of extra heat released in its assimilation. Just as there are several factors in the regulation of respiration, such as the CO_2 tension, the pH, the oxygen tension, these observations do not exclude the possibility that there may be other factors regulating food intake. Yet it appears that the intake of energy, as food, is to a large extent regulated indirectly via the heat liberated in metabolizing food. Since animals change their intake when the composition of food is altered (and this is not due to any of the more obvious dietary constituents including the caloric value of the food *per se*), this "intrinsic food factor is believed to be identical with the specific dynamic action" (SDA). The SDA is known to vary with the metabolic state of the animal, determined in part by the mixture which the animal consumes. The SDA is not the same as the sum of the specific dynamic actions of the individual constituents of the diet, but depends on the relative proportions of protein, fat, and carbohydrate. Perhaps this theory can be summed up in the following sentence: "All of these variations appear consistent with the idea that food intake is regulated by way of the extra heat produced in its assimilation, in that the intake decreases when the animals have difficulty in losing heat in a warm environment, or when heat production rises because of increased activity at a constant temperature."

It would seem that the nervous system drives or urges the individual to eat. This is apparent as restlessness and locomotion on searching for food. A satiated animal is not likely to discover more food because it fails to move about, and the urge to locomotion is an essential preliminary to feeding. In the human infant, restlessness, irritability, and crying serve the same purpose.

In terms of the hypothesis proposed, the SDA of food would play a role in the regulation of food intake analogous to the chemical changes which act centrally to modify respiratory exchange; and increases in the total amount of heat in the body, acting through thermal gradients and receptors, would initiate impulses which inhibit the mechanisms regulating feeding.

Although the concept that the SDA may play a role in the pathogenesis of obesity is not new, recent experimental data do suggest that this role may be of considerable importance, at least under some conditions.—S. O. WAIFE

The Consumption of Recommended Foods by Children in Relation to Sex, the Use of Sweet Foods, and Employment of Mothers. M. T. Doyle, M. C. Cahoon, and E. W. McHenry. *Canad. J. Pub. Health* 44: 259, 1953.

Grade school pupils in Canada, ranging in age from 11 to 15 years, and coming from a middle-class stratum in society, were studied by the dietary recall technique. From the records of almost 500 children, total intakes of food for the week were computed, divided by 7 to obtain average daily consumption, and an intake of one-half or less of a recommended quantity was rated as unsatisfactory. Cake, pastry, candy, sugar, and soft drinks were classified as sweet foods and an average daily consumption of three or more servings of these foods was rated as unsatisfactory. It was found that the proportion of children with unsatisfactory intake of various foods varied to a certain extent. Thus, about 25 per cent of the children had unsatisfactory milk intake; 40 per cent, citrus fruit; 50 per cent, vegetable; 74 per cent, cereals; and 90 per cent, vitamin D intake. (In the case of vitamin D, a record of daily use of any preparation likely to supply 400 units was considered satisfactory. This is a significant finding, in that 90 per cent of the children apparently ingested less than 400 units of vitamin D per day.) It is interesting that only 16 per cent had an unsatisfactory dietary history with respect to sweets; and only 5 per cent with respect to meat. There was little difference between the boys and girls in these individual items.

In the past three years there had been an educational campaign in the Toronto area on the use of sweet foods by children. A restriction had been urged for three reasons: there was evidence that a liberal use of these foods may promote dental caries; there was the assumption that sweet foods dull the appetite and may lessen the consumption of other foods; and there was a relatively poor return in nutritional value for the money spent on such foods. When the data were analyzed on the basis of the food intake of children having a liberal use of sweets as compared to those having a more sparing use of sweets, it appeared that of the 70 children who used sweet foods liberally, very similar, if not identical, percentages of unsatisfactory intakes were found as compared to the 374 children who used sweets sparingly. Thus, it does not appear that the liberal use of sweets necessarily interfered with the dietary intake of other foods.

Because a considerable number of children had mothers who were regularly employed outside the home, a comparison of food intake of the groups of children with or without employed mothers was made. No significant difference in use between the two groups was apparent. The authors say, "it does not seem that the absence of the mother from the home each working day made worse an already unsatisfactory picture of food use."—S. O. WAIFE

Food Supply, Body Weight and Activity in Great Britain, 1943–49. J. M. Harries and D. F. Hollingsworth. *Brit. Med. J.* 1: 75, 1953.

The problem of indices of the adequacy of food supplies for large population groups during times of war is an important one for the nutritionists. This paper describes some of the experiences of the British Ministry of Food during and after World War II. Body weights were followed in a sample of industrial workers and their wives. The age range was from 25 to 54 and the number varied from 3000 to 4500 individuals. Food consumption data were based on surveys which recorded the purchases of food and changes in larder stocks of a sample of the population which varied from 20,000 to 30,000 persons a year.

Between 1944 and 1948 the caloric intake per person fluctuated between 2800 and 3000 calories. Fluctuations in caloric intake were paralleled by similar trends in body weights. Mean body weight changes were small (2 to 6 lb.). In general, the observed population appeared to be roughly in caloric balance at 2900 calories, gained weight at 3000 calories and lost at 2800 calories. This evidence is advanced to support statements by the Ministry of Food in 1943 that a caloric level of 2800 calories is the minimum level necessary to sustain health in the general population. The authors recognize that any comparison between energy intake and body weight may be influenced by changes in the physical activity of the population. All attempts to devise indices of changing physical activity in the population under observation were considered failures. It is suggested that body weight surveys would provide an early index of the inadequacy of food supplies for large population groups.—H. L. TAYLOR

Degenerative Diseases with Nutritional Interrelationships. T. D. Spies. *Southern M. J.* 46: 238, 1953.

Examples drawn from clinical sources illustrate the idea that disease is chemical in nature and therefore can be corrected by chemical means if diagnosed early enough. Cases cited include the response of a pellagrin's magenta tongue to nicotinic acid; correction of pitting edema in a beriberi patient by thiamine; the relieving of rheumatoid arthritis and lip carcinoma by ACTH.

The examples are well chosen and excellently illustrated by the use of graphs and colored photographs. —M. W. BATES

Nitrogen Balance in Malignant Disease. N. Bolker. *Am. J. Roentgenol.* 69: 839, 1953.

The author has reviewed the literature on this subject and studied both nitrogen balance after irradiation of patients with nonmalignant disease, and nitrogen balance in a group of 25 patients with advanced malignant disease and absence of other sources of disturbance of nitrogen balance. Of the latter, 15 were cachectic and 10 were well nourished. The study indicated that the nitrogen intake is the principal factor regulating nitrogen balance. The nutritional state was the factor conditioning the nitrogen intake. All well-nourished patients easily accepted a high level of protein intake, but the cachectic patient did so with difficulty. The rate of nitrogen loss increased with increased nitrogen intake until a threshold was passed, after which these patients could achieve a positive equilibrium. Extravagant quantities of nitrogen were required to produce anabolism in the cachectic group. Individuals receiving protein hydrolysate intravenously were always in positive nitrogen balance during the period of administration. However, when the patients received protein supplements intravenously, the amount of protein taken orally was curtailed and the appetite for all types of food reduced.

Roentgen therapy uniformly caused a slight increase in urinary nitrogen, but to a lesser degree in the cachectic than in the well-nourished individuals. Irradiation has a depressing effect on nitrogen balance in both well-nourished and malnourished patients. The increased nitrogen output is believed to be due to breakdown of protein in tissues limited to the area of irradiation. In the series studied, all well-nourished patients with malignant disease were in positive nitrogen balance. Nitrogen deposit was apparently related to the high level of nitrogen intake common to the group. While the cause of the change from well-nourished to cachectic status is not known, its onset can be recognized by weight loss. The most accurate index of the onset of cachexia and its rate of progress is the nitrogen balance study, and the author suggests this as a consideration in the evaluation of the status of a patient with extensive malignant disease. It would appear that if the administration of a high level of nitrogen intake will inhibit or forestall cachexia, it might be of value in improving the effectiveness of radiation treatment and prolonging the life of the patient with extensive malignant disease.—G. T. Wohl

A Metabolic Study Following Extensive Resection of the Small Intestine for Sarcoma. H. Spencer, I. Lewin, and D. Laszlo. *Am. J. Med.* 14: 636, 1953.

The authors have long been engaged in metabolic studies in neoplastic diseases, with special interest in calcium and bone metabolism. In this paper they report the first prolonged (four-month) metabolic study of a patient following an extensive resection of the small intestine.

The 56-year-old patient had had a leiomyosarcoma of the descending colon removed 12 years ago. Three months before study, repeated episodes of subacute intestinal obstruction necessitated removal of 80 per cent of the small intestine for recurrent sarcoma. Metabolic study began during the fifth postoperative month. Uremia due to ureteral obstruction by recurrent tumor developed after termination of the study, and resulted in death three months later. At autopsy 135 cm. of upper jejunum, dilated to a circumference of 10 cm., were present.

During the study the patient was asymptomatic except for five bowel movements per day, and his weight remained nearly constant. On an average protein intake of 1.1 Gm. per Kg. the nitrogen balance was positive throughout, despite a high fecal nitrogen output. Sixty-eight per cent of the protein intake was absorbed. Stools weighed four times the normal control, contained eight times the normal water, and three times normal fat. Of ingested fat, 64 per cent was absorbed. The fecal electrolyte content approximated a plasma ultrafiltrate. The calcium balance followed the direction of the calcium intake.

The metabolic data indicated adequate absorption and utilization of nutrients. This was best shown by calcium balance studies; the negative calcium balance became increasingly positive with increasing calcium intake and the added calcium was normally utilized. The urinary calcium remained extremely low in spite of the high calcium intake, indicative of an attempt of the organism to conserve calcium to compensate for the loss of calcium in the stool. Failure to demonstrate impairment of absorption in the absence of most of the small bowel indicates that derangements of metabolism in malignancy depend on factors other than absorption.—J. Gruhn

The Effect of Varying Insulin Dosages on the Rate of Decline of the Blood Sugar in the Modified Glucose Insulin Tolerance Test. B. W. Volk and S. S. Lazarus. *J. Lab. & Clin. Med.* 41: 684, 1953.

Ten nondiabetics (normals?) were given 25 Gm. of glucose intravenously, followed by intravenous crystalline insulin after 30 minutes. Capillary blood sugar values were determined at fixed intervals before and after glucose and insulin. Comparison of the ten responses at each insulin dose (0.0, 0.01, 0.025, 0.05, 0.1, 0.2, 0.3 units per Kg. of body weight) discloses the following statistical inferences: no significant difference in rates of decline of blood sugar between 0 and 0.01 unit; significant ($P<0.05$) increase in rates of decline between 0.01, 0.025, and 0.05 dosage levels; no statistically significant differences in rates of decline at dosages exceeding 0.05 unit of insulin per Kg. The authors deduce that the dose of 0.1 unit of insulin per Kg. is probably optimal for assessment of insulin sensitivity by their method. No new data are advanced, however, which would suggest a means

of lessening the distinct danger of insulin tolerance tests in insulin-sensitive patients, such as those with diminished function of the adrenal cortex or of the anterior pituitary.—R. TARAIL

Medical Aspects of Hypoglycemia. P. G. Skillern and E. H. Rynearson. *J. Clin. Endocrinol.* 13: 587, 1953.

This is a review succinctly and comprehensively scanning the essential facts concerning hypoglycemia and freely utilizing the authors' vast experience. They encountered 6 patients with self-induced hypoglycemia due to the surreptitious injection of insulin. All had previous experience with insulin—3 as diabetic patients and 3 as nurses. The need for detective work in recognizing this unusual cause of hypoglycemia was emphasized. One author added typhoid vaccine to the patient's insulin bottle and another a radioactive material and demonstrated radioactivity of the urine. Fasting and exercise with the finding of a low blood sugar during the attack thus induced was found to be a more useful diagnostic procedure than glucose or insulin tolerance tests in the recognition of cases of hyperinsulinism due to functioning pancreatic island cell tumor. A meticulous search for a tumor should always be made, and if not found radical resection of the pancreas is warranted because the adenoma may be as small as 2 mm. in diameter. Hepatogenic hypoglycemia is not common and has been generally associated with extensive liver damage. Functional hypoglycemia is the most common type, the symptoms are less severe, less prolonged, less constant, and not progressive, in contrast to cases of insulin adenoma. A high protein, low carbohydrate diet generally ameliorates symptoms very efficiently.—N. G. SCHNEEBERG

Factors Determining Effect of Insulin on Metabolism of Glucose in Ascorbic Acid Deficiency and Scurvy in the Monkey. C. T. Stewart, R. J. Salmon, and C. D. May. *Am. J. Dis. Child.* 34: 677, 1952.

As part of a study of adrenocortical function in scurvy, the response of glucose to intravenous insulin was determined. In adrenal insufficiency, insulin produces sustained hypoglycemia; however, when insulin was administered intravenously to scorbutic monkeys, the level of glucose in the blood was never more than slightly depressed and frequently actually rose. This response indicates an increase in the adrenal cortical function and is contrary to what might have been expected. Other experiments on the influence of epinephrine and cortisone on the insulin response in scurvy suggest that adrenocortical function is *increased* rather than decreased in scorbutic monkeys.—S. O. WAIFE

Nontropical Sprue: Observations on Absorption and Metabolism. M. W. Comfort, E. E. Wollaeger, A. B. Taylor, and M. H. Power. *Gastroenterology* 23: 155, 1953.

Metabolic studies performed on 11 patients with non-tropical sprue revealed fecal excretion of fat, nitrogen, calcium, phosphorus, chloride, sodium, and potassium to be increased over normals. Fecal losses of fat and nitrogen were similar to those seen in pancreatic insufficiency. A parallelism was noted between the severity of the disease and the fecal losses of solids and electrolytes. Although larger intakes of fat, nitrogen, and calcium resulted in greater fecal loss of these substances, greater absorption was also observed. The authors conclude that the faulty absorption in non-tropical sprue affects a large number of metabolites and that the ideal diet for patients so affected should be high in calories, protein, carbohydrates and calcium, and low in fat.—S. H. LORBER

Sprue Syndromes and Their Cure With Folic Acid. L. Cannavò. *Acta vitaminol.* 6: 35, 1952.

In this "clinical lesson" the author delineates the features of a classical picture of sprue, as observed in a patient presenting the whole gamut of signs of this syndrome. The successful treatment was based on the concept that sprue is the result of a multiple vitamin deficiency, rather than of a deficit of folic acid alone. The following polyvitamin therapy was therefore employed: 20 mg. folic acid, 30 mg. riboflavin, 200 mg. nicotinamide, and 20 mg. thiamine daily. Examination of the patient one month later revealed complete remission of all pathologic signs. To insure maintenance of the patient's status, the following dosages were prescribed: 10 mg. folic acid, 100 mg. nicotinamide, 10 mg. thiamine, and 2 mg. riboflavin.—C.-J. HOWELL

Rates of Protein Synthesis, Amino Acid Catabolism and Size of Nitrogen Pool During Nitrogen Storage Induced with Testosterone Propionate and Testosterone Propionate Combined with Growth Hormone. P. D. Bartlett. *Endocrinology* 52: 272, 1953.

It has been previously shown by Bartlett that growth hormone reduces amino acid catabolism and increases the size of the nitrogen pool in the adult female dog. The present report deals with the effect of testosterone propionate alone or in combination with growth hormone upon various phases of protein metabolism. Testosterone accelerated protein synthesis and reduced amino acid catabolism but did not affect the size of the nitrogen pool. The combination with growth hormone caused nitrogen storage, weight gain, decreased amino acid catabolism, and a decrease in the size of the nitrogen pool. The author commented on the significance of these findings in relation to growth. Prepuberal growth is probably associated with a high rate of protein synthesis and degradation. Puberal growth (i.e., growth hormone plus testosterone, etc.) may be chiefly due to a lower rate of protein degradation and a lower total level of protein metabolism.—N. G. SCHNEEBERG

Essential Hyperlipemia. C. R. Joyner, Jr. *Ann. Int. Med.* 38: 759, 1953.

In this paper, thorough studies are reported on a patient with essential hyperlipemia. The literature on the subject is reviewed and hyperlipemia secondary to diseases such as renal vein thrombosis, nephrotic syndrome, hepatic disease, starvation, hypoproteinemia, anoxia, anemia, diabetes mellitus, von Gierke's disease, Niemann-Pick's disease, hypothyroidism, and pancreatic disease is discussed. When these diseases can be eliminated in a patient with sustained elevation of blood lipids, a diagnosis of essential hyperlipemia may be entertained. The condition affects males much more frequently than females. It has been found entirely in members of the Caucasian race. Eight cases have been described in children 16 years of age or younger and 13 cases in patients above the age of 20. Skin lesions similar to tuberous xanthoma and xanthoma diabeticorum have been reported in one-half of the cases. Abdominal pain and hepatosplenomegaly have been reported also in about 50 per cent of the cases. The abdominal pain is considered by most observers to be the result of rapid enlargement of the liver and spleen as a result of elevated blood lipid level. Lipemia retinalis has been observed in nine cases. A family history of hyperlipemia is noted occasionally in children, but has not been reported in adults.

The only laboratory findings of significance in idiopathic hyperlipemia are an elevation of neutral fat, a moderate increase in cholesterol, particularly the free fraction, and little or no change in the phospholipid level. Occasionally, glycosuria of a mild degree has been observed. Occasionally also, foam cells may be found in the sternal marrow and fatty vacuoles and foam cells in the liver parenchyma. Renal, liver, biliary, and endocrine functions have been essentially normal. It is generally considered that abnormal elimination of fat from the blood accounts for this hyperlipemia, but there is no explanation of why this occurs. Only one patient with idiopathic hyperlipemia has been autopsied, and there is no evidence as yet that these patients may be subject to early atherosclerosis. Low cholesterol diets will tend to lower blood lipid levels and will reduce the incidence of abdominal pain and hepatosplenomegaly. There is no other treatment of value at the present time.—R. W. VILTER

Physiologic Observations on a Case of Beriberi Heart Disease, with a Note on the Acute Effects of Thiamin. W. J. Lahey, D. B. Arst, M. Silver, C. R. Kleeman, and P. Kunkel. *Am. J. Med.* 14: 248, 1953.

The effects of thiamine deficiency and thiamine administration on the circulatory hemodynamics have been studied in a 29-year-old alcoholic addict by means of cardiac and renal vein catheterization. The patient was edematous, had ascites, hot extremities, a wide pulse pressure, elevated venous pressure and rapid circulation time. His electrocardiogram and heart size were normal. Before thiamine administration cardiac output was high, A-V oxygen difference small, and, in spite of the high venous pressure, the right auricular and ventricular pressures were only slightly elevated. The peripheral resistance was very low. Glomerular filtration rate and urine flow after a water load test were low. Within several hours after thiamine was given intravenously, changes took place of the following type: venous pressure fell, cardiac output decreased, and A-V oxygen difference increased. The pressure in the right auricle and ventricle did not change. Glomerulo-filtration rate increased, and urine-sodium diuresis occurred. At the end of 10 days the patient had lost 40 lb. and all evidence of congestion had disappeared. Recatheterization did not reveal any striking changes beyond those already reported.

These studies support the concept that the high venous pressure, small A-V oxygen difference, and low peripheral resistance are due to the dilated peripheral capillary bed which transmits arterial pressure unimpeded. There was no evidence in this patient for right-sided congestive failure to account for the elevated venous pressure. An increase in renal blood flow and/or efferent arteriolar constriction after thiamine could explain the improved glomerular filtration rate. However, lack of correlation in time of the various changes in renal function suggests that some factor other than renal hemodynamics explains the retention of sodium and water. The authors suggest that a volume-flow defect to the adrenal and posterior pituitary glands may play a role.

Obviously, heart failure frequently follows in a situation such as this, where the metabolism of the heart muscle is defective and the work load is so high. This patient's heart had not reached this point of decompensation.

This careful study adds considerable data confirmatory of many current theories concerning the pathologic physiology of beriberi heart disease.—R. W. VILTER

The Activation of Vitamin D of the Phosphorylation of Thiamin. C. E. Raiha and O. Forsander. *Science* 115: 242, 1952.

Intravenous or intramuscular thiamine increases the rate of phosphorylation of thiamine to cocarboxylase. Since vitamin D is related to phosphorus metabolism, clinical studies were performed to test the effect of vitamin D on this reaction. In some patients vitamin D strongly activated the synthesis of cocarboxylase. Younger subjects seem less prone to this activation than older ones. In other cases, there was no activation. This may have been due to the possibility of the subject's having been "saturated" with vitamin D before the experiment. In rickets, no activation is observed.—S. O. WAIFE

A Preliminary Study Concerning the Possibility of Dietary Carcinogenesis. R. Willheim and A. C. Ivy. *Gastroenterology* 23: 1, 1953.

In attempting to investigate gastric carcinogenesis, the authors studied the ability of 27 orally administered dyes to stain various portions of the gastrointestinal tract. Many stained the glandular portion of the stomach, but when feeding of a dye was discontinued the staining disappeared. The absorbed dyes were eliminated, at least partly, in the secretions of the gastric mucosa. Changes produced in the glandular portion of the stomach by dye administration included edema, poor staining of cells, vacuolization, and a loss of cytoplasmic pyrinophilia. Round cell infiltration was sometimes seen. Feeding of the dyes for from 6 to 20 months resulted in the development of lymphosarcoma of the lymphatic tissue in 7 of 33 animals. Five of 16 animals fed different dyes developed cirrhotic changes of the liver. Further investigation along these lines may prove fruitful in the search for an experimental gastric carcinogen.—S. H. Lorber

Body Build and Body Composition. J. Brožek and A. Keys. *Science* 116: 140, 1952.

The somatotype ratings of Sheldon are markedly affected by changes in nutritional status. The authors report on the relationship between somatotype ratings and specific gravity, in groups of men who have been on semistarvation nutritional experiments, to show a high coefficient of correlation. Specific gravity, as determined by weighing the body under water, gave an excellent estimation of the absolute and relative amounts of fat. The authors have developed equations for predicting total fatness on the basis of measurements of skinfolds which vary in thickness with the amount of subcutaneous adipose tissue.—M. K. Horwitt

Relative Body Weight, Age, and Fatness. J. Brožek and A. Keys. *Geriatrics* 8: 70, 1953.

The estimation of the amount of body fat by the specific gravity method and correlation with the standard height-weight tables in common use suggest that in a group of 273 clinically healthy men at all levels of relative underweight or overweight, the older men tended to be much fatter than the equivalent young men. This difference was approximately 15 per cent of body weight contributed by fat; furthermore, a comparison of the composition of the body of physically active and less active middle-aged men otherwise similar in height and age showed that the active individuals, although "overweight," were leaner. Their lean, or muscle, body mass contributed to their excess weight. Thus it would seem that the generally used relation of weight to height as a criterion of nutritional status in regard to calories is inadequate, since the individual's leanness-fatness (relative obesity) does not follow the standard weight curves.—S. O. Waife

Estimation of Lean Body Mass and Body Fat from Basal Oxygen Consumption and Creatinine Excretion. A. T. Miller, Jr. and C. S. Blyth. *J. Applied Physiol.* 5: 73, 1952.

College students with normal metabolism were the subjects in which body specific gravity, basal oxygen consumption and creatinine excretion were measured. Lean body mass (LBM) may be predicted from basal oxygen use according to the equation: LBM = 7.36 +0.2929 (oxygen), where LBM = lean body mass in Kg. and (oxygen) = basal oxygen use in ml./min. These results agree within ±10.5 per cent of the densiometric value in 90 per cent of cases. LBM may be predicted from the creatinine clearance according to the formula: LBM = 20.97 + 0.5161 (creatinine), where creatinine = urinary creatinine in mgm./hr. The results agree within ±13.1 per cent of the densiometric values in 90 per cent of cases. For groups of 50 or more, the prediction agreement in 90 per cent of the cases is ±1.5 per cent for O_2 and 2.0 per cent for creatinine. Correlation between relative body weight and body fat is poor.

It is pointed out that lean body mass is characterized by a constant rate of O_2 consumption; excretion of creatinine is correlated with lean body mass. Errors in O_2 consumption arise from fever, drugs, endocrine disturbances; in creatinine clearance from diet. Lean body mass is a much better basis for expression of metabolism, nutritional requirements, and drug dosage than total body weight.—M. J. Oppenheimer

Goiter Prevention with Iodized Salt, Results of a Thirty-Year Study. B. E. Brush and J. K. Altland. *J. Clin. Endocrinol.* 12: 1380, 1952.

The authors report on the results of a program of goiter prevention instituted in Michigan in 1923 emphasizing, through an education program carried out by the State Health Department and the State Medical Society, the value of iodized salt. The incidence of endemic goiter in 4 selected counties was reduced from 38.6 per cent in 1927 to 1.4 per cent in 1951. A striking inverse correlation was noted in the 1928 and 1935 surveys between the incidence of goiter and the use of iodized salt; in those using iodized salt the incidence was 2 to 3 per cent, whereas in a group not using it goiter was found in 25 to 35 per cent. This study is further confirmation of the well-known goiter-preventing properties of iodine first emphasized by Marine and Kimball in 1917. It must be emphasized, however, that iodine starvation is not the sole goitrogenic mechanism of clinical importance and iodine is of little value in the prevention or therapy of hyperplastic thyroid glands due to other mechanisms.—N. C. Schneeberg

Increased I^{131} Collection by the Thyroid of the Rat in Acute Starvation. B. Catz, I. El Rawi, and E. Geiger. *Am. J. Physiol.* 172: 291, 1953.

Rats were given a tracer dose of I^{131}. These animals were fasted for 24 hours and their thyroid glands then demonstrated an increased uptake of radioactive iodine. At this time, however, there was no change in the mean acinar cell height. Oral administration of 10 μg. of iodine to fasting animals returned iodine uptake to that observed in normal controls. Pure glucose without iodine to restore calories did not decrease the elevated I^{131} uptake noted in fasting animals. Forced feeding of water in fasting animals did not prevent an increased I^{131} uptake. The authors interpret these results to mean that the increased iodine uptake without structural change of the thyroid seen in fasting animals is due to acute dietary iodine deficiency.—M. J. Oppenheimer

Test of Chronic Toxicity of Iodine as Related to the Purification of Water. D. P. Morgan and R. J. Karpen. *U. S. Armed Forces M. J.* 4: 725, 1953.

In testing new compounds for the disinfection of small quantities of water, an iodine-releasing compound was found to meet best the requirements of the Armed Forces. Despite the superior germicidal properties of this compound, it was felt that the prolonged use of drinking water containing small amounts of iodine might have untoward effects on its users. Successful tests on small groups under artificial tropical conditions were followed by a field test at a naval installation in the Marshall Islands, where high temperature and humidity were constant. The station water system was chlorinated and treated with iodine for a period of 6 months. Average iodine dose per day per man was estimated at 12 mg. for the first 16 weeks; it was increased in the last 10 weeks of the study to an estimated 19.2 mg. Detailed examinations of 24 station personnel were made. Analysis of clinical findings revealed no significant pathological trends during consumption of iodated-chlorinated water. There was no evidence of weight loss, failure of vision, cardiovascular damage, altered thyroid activity, anemia, bone marrow depression, or renal irritation, nor was there any unusual incidence of skin disease. Wound healing and resolution of infections did not appear to be impaired, and there was no evidence of sensitization to iodine among healthy station personnel.—C. J. Howell

Fluorine in Human Nutrition. H. H. Mitchell and M. Edman. *J. Am. Dietet. A.* 29: 24, 1953.

Fluorine, the most reactive of the chemical elements, has never been demonstrated to be essential to animal life. Attempts to raise laboratory animals on synthetic rations containing minute concentrations of fluorine have been generally successful. If essential, the required concentration would seem to be less than 0.5 parts per million.

Its wide distribution in waters and minerals and in plant and animal tissues assures a constant supply for human nutrition. Fifty Gm. canned sardines may provide 0.8 mg. fluorine; one cup of tea may increase the fluorine of the diet by 0.2 mg. The use of fluoridated drinking water during the formative period of teeth is associated with a 60–65 per cent reduction in dental caries experience and about 75 per cent decrease in first permanent molar loss as compared with water containing traces of fluorine. The maximum effect will be realized at a concentration of 1.0–1.5 p.p.m. Water of this concentration causes an appreciable fluorine increase, 60 per cent in the dentine and 30 per cent in enamel. The successful experiences with fluoridation have resulted in a recommendation from the National Research Council in April 1951 that communities with water supplies free from or low in fluorides consider the practicability and economic feasibility of adjusting the concentration to optimal levels. The Council recommends adjustment in accord with climatic factors and constant chemical control. It is emphasized that this procedure should supplement, not supplant, other health measures.

Mitchell and Edman describe the conditions of mottled enamel, fluorotic osteosclerosis and industrial fluorosis with a discussion of their causation. It is estimated that daily intakes of about 15–20 mg. fluorine in the drinking water or in industrial exposure, over a period of several years, are required to induce chronic fluorosis in an adult man.—J. Smith

Influence of Tannic, Tartaric and of Acetic Acid upon Olfactory Acuity and Sensations Associated with Food Intake. D. L. Irvin and F. R. Goetzel. *Am. J. Dig. Dis.* 20: 17, 1953.

Dilute solutions of tannic, tartaric, and acetic acid were administered to subjects with, or in place of, the noon meal and the influence of these substances on olfactory acuity was measured. All of these acids were capable of preventing the usual postcibal decrease in olfactory acuity. They also interfered with creation of sensations interpreted as satiety. Although the effects of the acids upon olfactory acuity were statistically valid, one wishes that the authors had controlled their observations by the administration of water or some other substance in place of the acid.—S. H. Lorber

Action of Liver Extracts on Contractility of Isolated Mammalian Heart Muscle. J. P. Green. *Am. J. Physiol.* 170: 330, 1952.

Papillary muscles of cats were rendered hypodynamic by bathing in a low-calcium solution. Contractions of this preparation were increased by a petroleum ether extract of the non-saponifiable fraction of liver. The active material is water soluble, filterable, and dialyzable. Neither cholesterol nor carotene produces a similar effect.—M. J. Oppenheimer

Studies on the Relationship between Motility and Absorption in the Human Small Intestine. A. J. Cummins and T. P. Almy. *Gastroenterology* 23: 179, 1953.

The method of Nicholson and Chornock was employed to study intestinal absorption of glucose and methionine in 3 normals and 2 patients with sprue. Absorption of these materials by a 45 cm. segment of upper small bowel was increased by the administration of Urecholine® and physostigmine. Banthine®-induced hypomotility did not affect the shape of the glucose tolerance curve when glucose was introduced intraduodenally. The authors conclude that bowel hypomotility in sprue is not the primary cause of the poor absorption of glucose.—S. H. LORBER

Observations on Nature of Galactose Toxicity in Rats. J. M. Craig and C. E. Maddock. *Arch. Path.* 55: 118, 1953.

This paper clarifies the nature of the bone changes and the general toxicity of galactose. Galactose toxicity has previously been reported to produce galactosemia with roentgenologically demonstrable osteoporosis by pediatric investigators, cataracts by ophthalmologic investigators, and a multiplicity of pathologic sequelae.

The authors demonstrated that on a 70 per cent galactose-18 per cent casein diet, rats become relatively protein deficient in contrast with controls on 70 per cent glucose-18 per cent casein diets. Such animals excrete a high proportion of their ingested protein nitrogen. Peptides and amino acids are excreted in urine in increased amounts compared with glucose-fed controls. This increased nitrogen excretion is believed to have its origin in part in increased metabolic demand on the available nitrogen for gluconeogenesis and in part a competitive inhibition of amino acids and peptides by renal tubules which are saturated by galactose. The failure of galactose-fed animals to grow, corneal vascularization, iritis, lens cataract formation, testicular atrophy, and hydronephrosis are attributed to amino acid and protein deficiency. Tryptophane as added to the diets did not protect against cataracts. Neither the serum levels, the balance data on calcium and phosphorus metabolism, the postmortem roentgenologic survey, nor histologic sections of the bones revealed any significant deviation from normal in the formation or structure of the bone.

This is the best paper on galactose toxicity known to the reviewer.—J. GRUHN

Role of Acetoacetate in Aggravating the Disturbances in the Carbohydrate Metabolism of Scorbutic Animals. M. C. Nath, V. K. Sahu, and R. P. Chitale. *Biochem. J.* 53: 684, 1953.

It has previously been reported that vitamin C is necessary for glycogenesis and that its deficiency in the system brings about a marked depletion in glycogen content of the liver as well as of the muscle.

This work describes the increase in blood sugar and the rapid depletion in glycogen storage of guinea pigs which were completely denied vitamin C in their diet, and received daily acetoacetate in gradually increased amounts.

The fasting blood sugar values of normal and scorbutic guinea pigs did not differ significantly, but after administration of acetoacetate to the vitamin C-deficient guinea pigs there was observed a very appreciable rise in the blood sugar of the animals as well as a depletion in glycogen content of the liver and leg muscles. The low excretion of vitamin C in guinea pigs completely denied vitamin C and given acetoacetate was considered to be due to a destruction of vitamin C by acetoacetate *in vivo*.

Because of reports in the literature that low levels of vitamin C are associated with diabetes and that human diabetes is associated with a depletion of liver glycogen, the authors state that acetoacetate may be considered as one of the factors in the etiology of diabetes.—M. K. HORWITT